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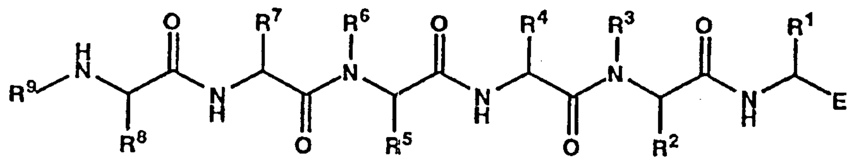

(I)

(57) Abstract

The invention provides amino acid derivatives of formula (I) wherein E represents CHO or $B(OH)_2$; R^1 represents lower alkyl (optionally substituted by halo, cyano, lower alkylthio, aryl–lower alkylthio, aryl or heteroaryl), lower alkenyl or lower alkynyl; R^2 represents lower alkyl optionally substituted by hydroxy, carboxy, aryl, aminocarbonyl or lower cycloalkyl; and R^3 represents hydrogen or lower alkyl; or R^2 and R^3 together represent di- or trimethylene optionally substituted by hydroxy; R^4 represents lower alkyl (optionally substituted by hydroxy, lower cycloalkyl, carboxy, aryl, lower alkylthio, cyano–lower alkylthio or aryl–lower alkylthio), lower alkenyl, aryl or lower cycloalkyl; R^5 represents lower alkyl (optionally substituted by hydroxy, lower alkylthio, aryl, aryl–lower alkylthio or cyano–lower alkylthio) or lower cycloalkyl; R^6 represents hydrogen or lower alkyl; R^7 represents lower alkyl (optionally substituted by hydroxy, carboxy, aryl or lower cycloalkyl) or lower cycloalkyl; R^8 represents lower alkyl optionally substituted by hydroxy, carboxy or aryl; and R^9 represents lower alkylcarbonyl, carboxy–lower alkylcarbonyl, arylcarbonyl, lower alkylsulphonyl, arylsulphonyl, lower alkoxycarbonyl or aryl–lower alkoxycarbonyl, and salts of acidic compounds of formula (I) with bases, which are viral proteinase inhibitors useful as antiviral agents, especially for the treatment or prophylaxis of infections caused by Hepatitis C, Hepatitis G and human GB viruses.

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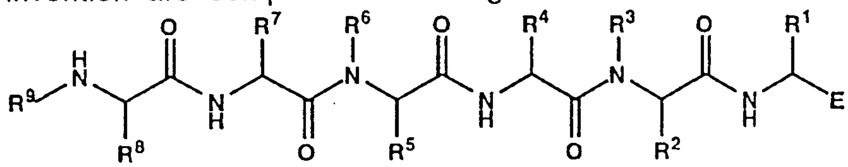
ANTIVIRAL PEPTIDE DERIVATIVES

The present invention is concerned with amino acid derivatives and a process for their manufacture.

The amino acid derivatives provided by the present invention are compounds of the general formula



(I)

wherein

E	represents CHO or $B(OH)_2$;
R^1	represents lower alkyl, halo-lower alkyl, cyano-lower alkyl, lower alkylthio-lower alkyl, aryl-lower alkylthio-lower alkyl, aryl-lower alkyl, heteroaryl-lower alkyl, lower alkenyl or lower alkynyl;
R^2	represents lower alkyl, hydroxy-lower alkyl, carboxy-lower alkyl, aryl-lower alkyl, aminocarbonyl-lower alkyl or lower cycloalkyl-lower alkyl; and
R^3	represents hydrogen or lower alkyl; or
R^2 and R^3	together represent di- or trimethylene optionally substituted by hydroxy;
R^4	represents lower alkyl, hydroxy-lower alkyl, lower cycloalkyl-lower alkyl, carboxy-lower alkyl, aryl-lower alkyl, lower alkylthio-lower alkyl, cyano-lower alkylthio-lower alkyl, aryl-lower alkylthio-lower alkyl, lower alkenyl, aryl or lower cycloalkyl;
R^5	represents lower alkyl, hydroxy-lower alkyl, lower alkylthio-lower alkyl, aryl-lower alkyl, aryl-lower alkylthio-lower alkyl, cyano-lower alkylthio-lower alkyl or lower cycloalkyl;
R^6	represents hydrogen or lower alkyl;
R^7	represent lower alkyl, hydroxy-lower alkyl, carboxy-lower alkyl, aryl-lower alkyl, lower cycloalkyl-lower

alkyl or lower cycloalkyl;

R^8 represents lower alkyl, hydroxy-lower alkyl, carboxy-lower alkyl or aryl-lower alkyl; and

R^9 represents lower alkylcarbonyl, carboxy-lower alkylcarbonyl, arylcarbonyl, lower alkylsulphonyl, arylsulphonyl, lower alkoxycarbonyl or aryl-lower alkoxycarbonyl;

and salts of acidic compounds of formula I with bases.

The compounds of formula I and their aforementioned salts inhibit proteinases of viral origin and are useful in the treatment of viral infections, particularly viral infections caused by Hepatitis C, Hepatitis G and the human GB viruses.

As used in this specification, the term "lower alkyl", alone or in combination, denotes a straight-chain or branched chain alkyl group preferably containing 1-7, especially 1-4, carbon atoms, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec.butyl, tert.butyl, n-pentyl, neopentyl and the like. "The terms "lower alkenyl" and "lower alkynyl" denote alkenyl groups preferably containing 2-7 carbon atoms, e.g. vinyl, allyl, n-propenyl, n-butenyl, and the like, and, respectively, alkynyl groups preferably containing 2-7 carbon atoms, e.g. propargyl and the like. The term "lower cycloalkyl" denotes a cycloalkyl group preferably containing 3-7 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl and the like. The lower alkoxy part of a "lower alkoxycarbonyl" group is preferably a lower alkyl ether group in which the lower alkyl moiety has the aforementioned significance. The term "aryl" denotes a monocyclic or polycyclic aromatic hydrocarbon group, e.g. phenyl, naphthyl or the like which is unsubstituted or substituted by one or more substituents selected from e.g. lower alkyl, lower alkoxy, nitro, halo, halo-lower alkyl, hydroxy, acetamido and the like. The term "heteroaryl" denotes a 5- or 6-membered aromatic heterocyclic group which contains N, O and/or S as the hetero atom(s) and which is optionally benz-fused and/or substituted in the same manner as the aryl group defined above. Examples of heteroaryl groups are furyl, thienyl, pyridyl, pyrimidinyl, benzofuranyl,

benzothienyl, quinolyl, isoquinolyl and the like.

The compounds of formula I contain at least six asymmetric carbon atoms and can therefore exist in the form of optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates or mixtures of diastereoisomeric racemates. The present invention includes within its scope all of these possible forms.

One class of preferred compounds of formula I comprises those in which R^1 represents lower alkyl, halo-lower alkyl, lower alkylthio-lower alkyl, aryl-lower alkylthio-lower alkyl, heteroaryl-lower alkyl, lower alkenyl or lower alkynyl. Fluoro-lower alkyl is the preferred halo-lower alkyl group. Preferred heteroaryl-lower alkyl groups are thienyl-lower alkyl and furyl-lower alkyl. Preferably, R^2 represents lower alkyl, lower cycloalkyl-lower alkyl or aryl-lower alkyl and R^3 represents hydrogen or R^2 and R^3 together represent trimethylene optionally substituted by hydroxy. R^4 preferably represents lower alkyl, lower cycloalkyl-lower alkyl, aryl-lower alkyl, aryl or lower cycloalkyl, R^5 preferably represents aryl-lower alkyl or lower cycloalkyl, R^6 preferably represents hydrogen, R^7 preferably represents lower alkyl, carboxy-lower alkyl, aryl-lower alkyl or hydroxy-lower alkyl, R^8 preferably represents hydroxy-lower alkyl, carboxy-lower alkyl or aryl-lower alkyl and R^9 preferably represents lower alkylcarbonyl or carboxy-lower alkylcarbonyl.

Examples of these preferred compounds in which E represents CHO are:

2(S)-[[N-[N-[N-[N-[N-(3-Carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]butyraldehyde;

2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4-difluorovaleraldehyde;

2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-

leucyl]amino]-4,4,4-trifluorobutyraldehyde;

2(R)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-3-(methylthio)propionaldehyde;

2(R)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-3-(butylthio)propionaldehyde;

2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4-pentenaldehyde;

2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4-pentynal;

2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4-hexynal;

3-(benzylthio)-2(R)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]propionaldehyde;

2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-3-(2-thienyl)propionaldehyde;

2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-3-(3-thienyl)propionaldehyde;

2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-3-(2-naphthyl)-D-alanyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde;

2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-seryl-D-valyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]-amino]-4,4,4-trifluorobutyraldehyde;

2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]hexanal;

(Z)-2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4-hexenal;

2(RS)-[[N-[N-[N-[N-[N-(benzyloxycarbonyl)-L-α-aspartyl]-L-

α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde;

2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-4-chloro-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde;

2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-D-valyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde;

2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-5-methylhexanal;

2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-5-hexenal;

2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-D-norleucyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde;

2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-D-2-cyclohexylglycyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde; and

2(RS)-[[N-[N-[N-[N-[N-(4-acetamidobenzoyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde;

and examples of these preferred compounds in which E represents $B(OH)_2$ are:

1(RS)-[[N-[N-[N-[N-[N-(3-Carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]propylboronic acid;

1(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]butylboronic acid;

1(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-3-butenylboronic acid;

1(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-4-chloro-2-methyl-L-phenylalanyl]-3-methyl-L-

valyl]-L-leucyl]amino]-3-butenylboronic acid;

1(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-3-cyclopentyl-L-alanyl]amino]-3-butenylboronic acid;

1(R)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]pentylboronic acid;

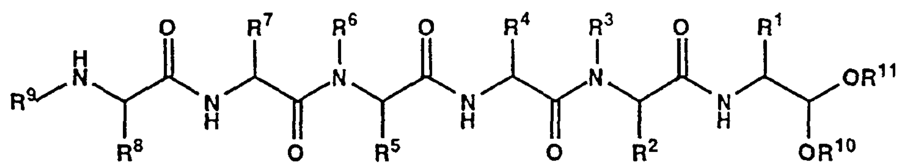
1(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-L-2-cyclohexylglycyl]-L-leucyl]amino]propylboronic acid;

1(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-L-2-cyclohexylglycyl]-3-methyl-L-valyl]-L-leucyl]amino]propylboronic acid; and

1(RS)-[[N-[N-[N-[N-[N-(benzyloxycarbonyl)-L-α-aspartyl]-D-valyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl-L-leucyl]-amino]propylboronic acid.

According to the process provided by the present invention, the compounds of formula I hereinbefore and salts of acidic compounds of formula I with bases are manufactured by

a) for the manufacture of a compound of formula I in which E represents CHO, deacetalizing and, where required, deprotecting an acetal of the general formula



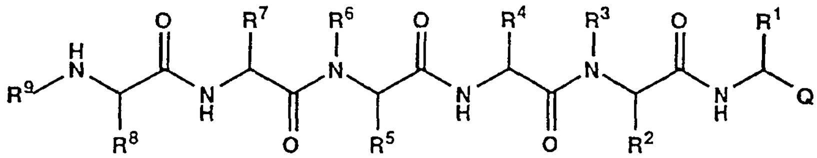
(II)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 have the significance given earlier, provided that any carboxy, hydroxy and/or aminocarbonyl group(s) present is/are in protected form, and R^{10} and R^{11} each represent lower alkyl,

or

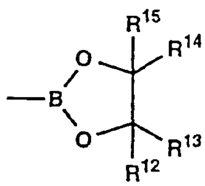
b) for the manufacture of a compound of formula I in which E represents $B(OH)_2$, ring opening and, where required, deprotecting

a substituted dioxaborolane of the general formula



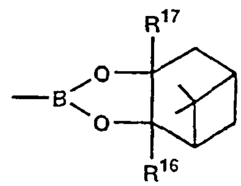
(III)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 have the significance given earlier, provided that any carboxy, hydroxy and/or aminocarbonyl group(s) present may be in protected form, and Q represents a group of the formula



(a)

or



(b)

wherein R^{12}, R^{13}, R^{14} and R^{15} each represent hydrogen or lower alkyl and R^{16} and R^{17} each represent hydrogen or lower alkyl,

and

c) if desired, converting an acidic compound of formula I obtained into a salt with a base.

Protected carboxy, hydroxy and aminocarbonyl groups which are present in the acetal starting materials of formula II and which may be present in the substituted dioxaborolane starting materials of formula III are carboxy, hydroxy and, respectively, aminocarbonyl groups protected with a conventional protecting group known from peptide chemistry. In particular, R^2, R^4, R^7, R^8 and/or R^9 can preferably represent tert-butoxycarbonyl-lower alkyl as protected carboxy, R^2, R^4, R^5, R^7 R^8 and/or R^9 can preferably represent lower alkyl O-tert.butyl ether as protected hydroxy and R^2 can preferably represent tritylaminocarbonyl-lower alkyl as protected aminocarbonyl-lower alkyl.

The deacetalization of an acetal of formula II, preferably one in which R^{10} and R^{11} each represent methyl, according to embodiment a) of the process according to the invention can be carried out in a manner known per se. It is conveniently effected using trifluoroacetic acid or an equivalent strong acid in the presence of an inert organic solvent such as a halogenated aliphatic hydrocarbon, e.g. dichloromethane, and in the presence of water. Suitably, the deacetalization is carried out at about room temperature. When protected carboxy, hydroxy and/or aminocarbonyl groups are present in the acetal starting material, these are converted into free carboxy, hydroxy and/or amino-carbonyl groups under the conditions of the deacetalization.

According to a variant of embodiment a) of the process according to the invention, an acetal starting material of formula II is bonded to a solid phase peptide synthesis resin. In this case, cleavage from the resin takes place under the conditions used for the deacetalization.

The ring opening of a substituted dioxaborolane of formula III in which Q represents a group of formula (a), preferably one in which R^{12}, R^{13}, R^{14} and R^{15} each represent methyl, according to embodiment b) of the process according to the invention can also be carried out in a manner known per se. Conveniently, the ring opening is carried out using trifluoroacetic acid or an equivalent strong acid in an inert organic solvent, e.g. a halogenated aliphatic hydrocarbon such as dichloromethane, and optionally in the presence of water. Suitably, the ring opening is carried out at about room temperature. When protected carboxy, hydroxy and/or aminocarbonyl groups are present in the substituted dioxaborolane starting material, these are converted into free carboxy, hydroxy and/or aminocarbonyl groups under the conditions of the ring opening.

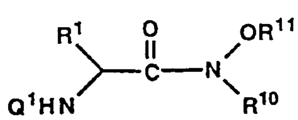
The ring opening of a substituted dioxaborolane of formula III in which Q represents a group of formula (b), especially one in which one of R^{16} and R^{17} represents hydrogen and the other

represents methyl, according to embodiment b) of the process in accordance with the invention can be carried out in a conventional manner. Conveniently, the ring opening is carried out using a periodate, especially an alkali metal periodate, especially sodium periodate in a buffered aqueous-organic medium, suitably at about room temperature. Advantageously, the medium consists of a mixture of an inert water-miscible organic solvent, e.g. acetone, and aqueous ammonium acetate. Any protected carboxy, hydroxy and/or aminocarbonyl group(s) present in the substituted dioxaborolane starting material are deprotected in a manner known per se, e.g. by treatment with trifluoroacetic acid, prior to the ring opening.

According to a variant of embodiment b) of the process according to the invention, a substituted dioxaborolane of formula III in which Q represents a group of formula (a) is bonded to a solid phase synthesis resin. The bonding is typically through an alkyl group R^{12}, R^{13}, R^{14} or R^{15} linked to the resin via an amide bridge. Cleavage from the resin takes place under the conditions used in embodiment b) of the process.

In accordance with embodiment c) of the process acidic compounds of formula I can be converted into salts with bases, e.g. alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as calcium or magnesium salts, salts with organic bases, e.g. salts with amines such as N-ethylpiperidine, procaine or dibenzylamine, or salts with basic amino acids such as salts with arginine or lysine. The formation and isolation of such salts can be carried out according to methods known per se.

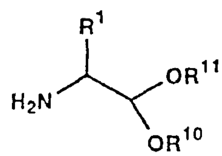
The acetal starting materials of formula II are novel and also form an object of the present invention. They can be prepared, for example, by firstly reducing a hydroxamate of the general formula



(IV)

wherein R^1, R^{10} and R^{11} have the significance given earlier and Q^1 represents an amino protecting group, e.g. tert.butoxycarbonyl,

with an alkali metal aluminium hydride, e.g. lithium aluminium hydride, treating the product with methanolic hydrochloric acid to give the hydrochloride salt of a compound of the general formula



(V)

wherein R^1, R^{10} and R^{11} have the significance given earlier, and subsequently either subjecting this to sequential coupling with respective amino acids or subjecting a fragment obtained during such a sequential coupling to further coupling with a peptide derivative of appropriate length. Alternatively, a compound of formula V can be coupled with a suitable pentapeptide.

The aforementioned coupling reactions can be carried out in a manner known per se in peptide chemistry, conveniently using the respective amino acid or di, tri-, tetra- or pentapeptide appropriately protected as described above and also at any amino group present by Fmoc [(9-fluorenyl)methoxycarbonyl] in the presence of hydroxybenzotriazole, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and N-methylmorpholine and in an inert organic solvent, e.g. a halogenated hydrocarbon such as dichloromethane.

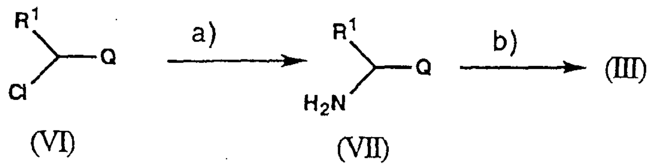
The hydroxamates of formula IV required for the preparation of the acetal starting materials of formula II are known compounds or analogues of known compounds which can be prepared in an analogous manner to the known compounds.

The acetal starting materials of formula II can also be synthesised from a compound of formula V on a solid phase peptide synthesis resin. This procedure is known and is described

in detail in Handbook from Fourth International Symposium on Solid Phase Synthesis and Combinatorial Chemical Libraries, Edinburgh, 1995.

The substituted dioxaborolanes of formula III used as starting materials in embodiment b) of the process according to the invention are novel and form a further object of the present invention. They can be prepared, for example, as illustrated in Scheme A hereinafter in which R^1 and Q have the significance given earlier:

Scheme A



Having regard to Scheme A, in step a) a compound of formula VI is reacted with an alkali metal bis[tri(lower alkyl)silyl]amide, e.g. lithium bis(trimethylsilyl)amide, in an inert organic solvent such as an ether, e.g. diethyl ether or tetrahydrofuran, and then treated with a strong acid, e.g. trifluoroacetic acid, to give a compound of formula VII.

In step b) a compound of formula VII is converted into a compound of formula III either by coupling with a pentapeptide, by sequential coupling with respective amino acids or by coupling a fragment obtained during the sequential coupling with a peptide derivative of the desired length, with the amino acid or peptide used being appropriately protected as described above and also at any amino group present by Fmoc. These coupling reactions can be carried out in a manner known per se in peptide chemistry, for example using the amino acid or peptide in the form of a mixed anhydride formed e.g. with a lower alkyl haloformate such as isobutyl chloroformate and carrying out the coupling in the presence of a suitable base, e.g. a tertiary organic base such as N-methylmorpholine.

Substituted dioxoborolanes of formula III obtained by the foregoing coupling and which carry a protecting group on the substituent at R^2, R^4, R^5, R^7, R^8 and/or R^9 can be selectively deprotected in a conventional manner, e.g. using trifluoroacetic acid, to the corresponding compounds which carry a free carboxy, hydroxy and/or aminocarbonyl group on the respective substituent, while retaining the protected boronic acid moiety denoted by Q. These selectively deprotected compounds are also active as inhibitors of proteinases of viral origin and can be used in the treatment of viral infections in the same manner as the compounds of formula I

Compounds of formula VI can be prepared, for example, from a compound of the general formula

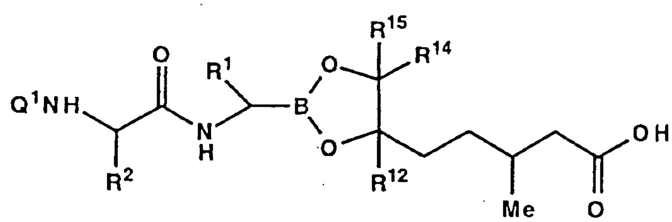
$$Cl_2CH\text{-}Q \qquad \text{(VIII)}$$

wherein Q has the significance given earlier, which is a known compound or an analogue of a known compound, by reaction with a compound of the formula R^{1a}-MgHal, wherein R^{1a} has the same significance as R^1 hereinbefore, but contains one carbon atom less and Hal represents halogen, preferably bromine. The reaction is carried out under the conventional conditions of a Grignard reaction, for example in an inert organic solvent such as an ether, e.g. diethyl ether or tetrahydrofuran. When Q represents a group of formula (b), the reaction is carried out in the presence of zinc chloride.

A compound of formula VI in which R^1 represents bromo-lower alkyl or fluoro-lower alkyl and Q represents a group of formula (a) can be prepared, for example, by hydroborating a bromo- or fluoro-lower alkene, e.g. 3-bromopropene or 3-fluoropropene, reacting the hydroboration product with a diol of the formula $R^{12}R^{13}C(OH)\text{-}C(OH)R^{14}R^{15}$, wherein R^{12}, R^{13}, R^{14} and R^{15} have the significance given earlier, e.g. 2,3-dimethyl-2,3-butanediol, and reacting the resulting 2-(bromo- or fluoro-lower alkyl)-1,3,2-dioxaborolane with dichloromethane in the presence

of lithium diisopropylamine. The hydroboration can be carried out in a conventional manner, for example using phenylboronic acid at an elevated temperature, e.g. about 100°C, in the absence of a solvent or using borane-dimethyl sulphide complex in the presence of cyclohexene in an inert organic solvent, e.g. dimethoxyethane, at about 0°C followed by treatment with trimethylamine N-oxide.

A substituted dioxoborolane of formula III in which Q represents a group of formula (a) can also be synthesised on a solid phase peptide synthesis resin. For example, a 4-methyl-benzhydryl resin can be reacted with a dioxoborolanyl-valeric acid of the general formula

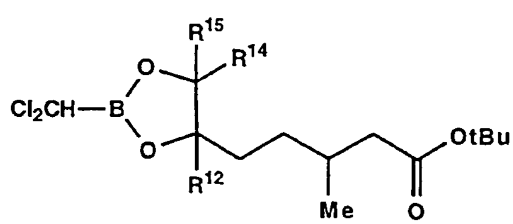


(IX)

wherein R^1, R^2, R^{12}, R^{14}, R^{15} and Q^1 have the significance given earlier,

and the product can be converted into the required resin-bonded starting material by successive deprotection and coupling with a protected amino acid.

Compounds of formula IX can be conveniently prepared by reacting a tert-butyl 6,7-dihydroxy-3,6,7-tri(lower alkyl)-6-octenoate with dichloromethyl diisopropoxyborane, condensing the resulting compound of the general formula

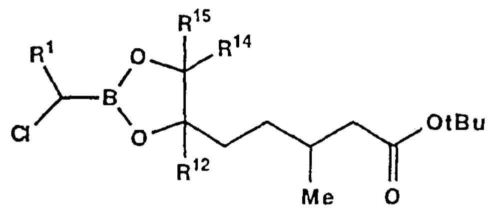


(X)

wherein R^{12}, R^{14} and R^{15} have the significance given

earlier,

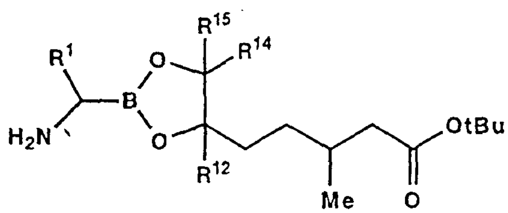
with a compound of formula R^1MgHal, wherein R^1 has the significance given earlier and Hal represents halogen, preferably bromine, under the conditions of a Grignard reaction, reacting the resulting compound of the general formula



(XI)

wherein R^1, R^{12}, R^{14} and R^{15} have the significance given earlier,

with an alkali metal bis[tri(lower alkyl)silyl]amide, condensing the resulting compound of the general formula



(XII)

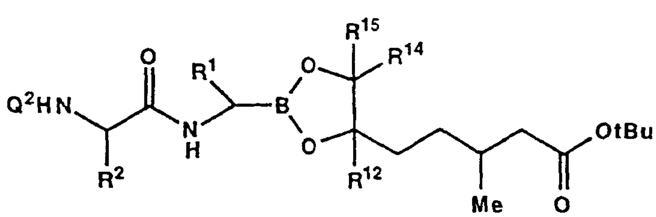
wherein R^1, R^{12}, R^{14} and R^{15} have the significance given earlier,

with a protected amino acid of the general formula

$$Q^2HN\text{-}CH(R^2)\text{-}COOH \qquad (XIII)$$

wherein R^2 has the significance given earlier and Q^2 represents Fmoc,

and de-esterifying the resulting compound of the general formula



(XIII)

wherein R^1, R^2, R^{12}, R^{14}, R^{15} and Q^2 have the significance given earlier.

As mentioned earlier, the compounds of formula I and salts of acidic compounds of formula I with bases are inhibitors of proteases of viral origin. The activity against one such protease, namly HCV protease, can be demonstrated using the following assay:

<u>Construction of plasmid for the expression of MBP-NS3"Gly $_{12}$-NS4A enzyme in E. coli</u>

The nucleotide sequence of this expression plasmid is given in Figure 1 appended hereto and the amino acid sequence of its expression product is given in Figure 2 appended hereto. It is based on the pMAL®-c2 vector supplied by New England Biolabs, Inc. (32 Tozer Rd., Beverly, MA, USA). The principle of the construction was to create an in-frame fusion of the maltose binding protein (MBP) gene supplied by the pMAL-c2 vector, and sequences of the HCV genome necessary for NS3 proteinase activity. These HCV sequences were inserted between the EcoRI and HindIII sites of the pMAL-c2 polylinker (positions 2695 and 3556 respectively of the sequence given in Figure 1).

HCV sequences were derived from plasmids pDS 3348-4045 and pBFK 3348-6062, described by Bartenschlager et al, 1993 (Journal of Virology, 67, 3835-3844). Regions encompassing the NS3 proteinase domain (amino acids 1007-1219) and the NS4A domain (amino acids 1658-1711) were isolated and inserted into the pMAL-c2 vector using standard recombinant DNA techniques, including the PCR amplification of required sequences. Between the NS3 and NS4A domains, a linker region was constructed using synthetic oligonucleotides (positions 3343-3390; amino acids 606-621). The resulting plasmid was used to transform E. coli (strain MC1061) cells and expression of the MBP-NS3"Gly $_{12}$-NS4A enzyme was induced as described below.

Protein expression and purification

E. coli (strain MC1061) cells transformed with the foregoing plasmid were grown in Luria broth containing ampicillin (100 µg/ml) at 37°C. The cells were grown until an optical density of 0.5 at 600 nm had been reached and enzyme expression was then induced by adding 1 mM isopropylthiogalactoside and incubating at 37°C for a further 3 hours. The cells were harvested by centrifugation and stored at -80°C.

A pellet from 4 l of bacterial culture was resuspended in E.coli lysis buffer (20 mM Tris HCl, pH 7.5, containing 150 mM NaCl, 1mM EDTA and 10 mM dithiothreitol) and cell lysis was achieved by two passages through a French Pressure cell. The clear supernatant obtained by centrifugation (18000 g, 30 minutes) was then applied to an amylose resin column (4 x 1 cm) (New England Biolabs) which had been equilibrated with ice-cold 50 mM Tris HCl, pH 8.5, containing 200 mM NaCl, 1 mM dithiothreitol and 5% glycerol. The column was washed thoroughly with the equilibration buffer and bound protein was eluted using the equilibration buffer containing 10 mM maltose. Fractions of 1 ml were collected, with fractions containing the enzyme being pooled and stored at -80°C. Enzyme concentration was assayed by the method of M.B. Bradford, Analytical Biochemistry, 1976, vol. 72, p.248.

Assay

Compounds of formula I (routinely prepared as stock solutions in DMSO) were assayed for their ability to inhibit the cleavage of a quenched fluorescence substrate [NS4A/B.F peptide (N-[4-[4-(dimethylamino)phenylazo]benzoyl]-L-α-aspartyl-L-α-glutamyl-L-methionyl-L-α-glutamyl-L-α-glutamyl-L-cysteinyl-L-alanyl-L-seryl-L-histidyl-N5-[2-(5-sulpho-1-naphthylamino)-ethyl]-L-glutaminamide); Wilkinson et al, Society for General Microbiology Meeting, University of Warwick, England, 28 March 1996] based on the NS4A/4B cleavage site by enzyme MBP-NS3"Gly $_{12}$-NS4A in microtitre plates as follows:

The enzyme (1 μg) was added to 200 μl final volume of a mixture containing 50 mM Tris HCl, pH 8.5, with 1mM dithiothreitol, 0.1% Triton X-100 and the test compound of formula I. The resulting mixture was incubated at room temperature for 15 minutes prior to starting the reaction by the addition of NS4A/B.F peptide to a final concentration of 10 μM. The progress of the reaction was evaluated with a Perseptive Biosystems Cytofluor II using an excitation wavelenth of 360 nm and an emission wavelength of 530 nm. After incubation for a further 10 minutes, the reduction in fluorescence in the presence of inhibitor was measured. This was plotted against inhibitor concentration and the inhibitor concentration which caused 50% reduction (IC_{50}) was calculated by manual graphical analysis or by the use of the Perseptive Biosystems Cytocalc curve fitting program.

The results obtained in the foregoing assay with representative compounds of formula I are compiled in the following Table:

Table

Compound of formula I	HCV proteinase IC_{50} (μmol/l)
A	0.09
B	0.07
C	0.064
D	0.034
E	0.038
F	0.16

Compounds:

A = 2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4-pentenaldehyde.

B = 2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4-difluorovaleraldehyde.

C = 2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde.

D = 1(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-3-butenylboronic acid.

E = 1(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]propylboronic acid.

F = 1(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]butylboronic acid.

The compounds of formula I and salts of acidic compounds of formula I with bases can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered enterally such as orally in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, nasally, e.g. in the form of nasal sprays, or rectally, e.g. in the form of suppositories. They may, however, also be administered parenterally, e.g. in the form of injection solutions.

The compounds of formula I and their aforementioned salts can be processed with pharmaceutically inert, organic or inorganic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts and the like can be used, for example, as such carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like; depending on the nature of the active ingredient no carriers are, however, usually required in the case of soft gelatine capsules. Suitable carriers for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar, glucose and the like. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

The pharmaceutical preparations can also contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

Medicaments containing a compound of formula I or a salt of an acidic compound of formula I with a base in association with a compatible pharmaceutical carrier are also an object of the present invention, as is a process for the production of such medicaments which comprises bringing one or more of these compounds or salts and, if desired, one or more other therapeutically valuable substances into a galenical administration form together with a compatible pharmaceutical carrier.

As mentioned earlier, the compounds of formula I and salts of acidic compounds of formula I with bases can be used in accordance with the invention as therapeutically active substances, especially as antiviral agents. The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of administration to adults a convenient daily dosage should be about 3 mg to about 3 g, preferably about 10 mg to 1 g. The daily dosage may be administered as a single dose or in divided doses and, in addition, the upper dosage limit referred to earlier may be exceeded when this is found to be indicated.

Finally, the use of compounds of formula I and salts of acidic compounds of formula I with bases for the production of medicaments, especially of antiviral medicaments, is also an object of the invention.

The invention is illustrated by the following Examples. In the Examples SSA denotes the solvent system 0.1% TFA in water and SSB denotes the solvent system 0.1% TFA in 70% acetonitrile 30% water.

Example 1

0.1 g (0.1 mmol) of N2-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(S)-(dimethoxymethyl)propyl]-L-leucinamide was dissolved in 3 ml of dichloromethane, 3 ml of trifluoroacetic acid and 90 mg of water and the mixture was stirred at room temperature for 30 minutes. The solution was diluted with 20 ml of toluene and the solvent was removed by evaporation. The resulting white solid was triturated with diethyl ether and filtered off. The solid was purified by RP-HPLC on a C18 Dynamax column (pore size 300Å; column size 21.4 mm x 50 mm). The elution gradient comprised 90% SSA 10% SSB to 95% SSB 5% SSA over 8.5 minutes. After lyophilization overnight there were obtained 25 mg of 2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]butyraldehyde as a white foam. MS: m/e 819.5 $[M+H]^+$.

The starting material was prepared as follows:

i) A solution of 25 g (63.6 mmol) of L-leucine benzyl ester p-toluenesulphonic acid salt, 14.69 g (63.6 mmol) of N-(tert-butoxycarbonyl)-3-methyl-L-valine, 9.73 g (63.6 mmol) of 1-hydroxybenzotriazole, 7.32 g (63.3 mmol) of N-ethylmorpholine and 12.21 g (63.6 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride in 500 ml of dichloromethane was stirred at room temperature overnight. The solution was washed with water, sodium hydrogen carbonate solution, 2M hydrochloric acid and saturated sodium chloride solution and dried over anhydrous magnesium sulphate. Evaporation gave 21.65 g of N-[(N-tert-butoxycarbonyl)-3-methyl-L-valyl]-L-leucine benzyl ester as an oil which was used in the next step without further purification. MS: m/e 435 $[M+H]^+$.

ii) A solution of 9.74 g (22.4 mmol) of N-[(N-tert-butoxycarbonyl)-3-methyl-L-valyl]-L-leucine benzyl ester in 25 ml of

trifluoroacetic acid and 50 ml of dichloromethane was stirred at room temperature for 30 minutes. The solvent was removed by evaporation and 50 ml of toluene were added. Evaporation gave N-(3-methyl-L-valyl)-L-leucine benzyl ester as an oil which was used in the next step without further purification.

iii) A solution of the foregoing oil, 9 g (22.4 mmol) of N-(9-fluorenylmethoxycarbonyl)-2-methyl-L-phenylalanine, 3.43 g (22.4 mmol) of 1-hydroxybenzotriazole, 3.87 g (33.66 mmol) of N-ethylmorpholine and 4.31 g (22.4 mmol) of 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride in 100 ml of dichloromethane was stirred at room temperature overnight. The solution was washed with water, sodium hydrogen carbonate solution, 2M hydrochloric acid and saturated sodium chloride solution and dried over anhydrous magnesium sulphate. Evaporation and chromatography on silica gel using 30% ethyl acetate in petroleum ether (b.p. 40-60°C) for the elution gave 12.32 g of N-[N-[N-[(9-fluorenyl)methoxycarbonyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine benzyl ester as an oil. MS: m/e 718 $[M+H]^+$.

iv) A solution of 10 g (13.95 mmol) of N-[N-[N-[(9-fluorenyl)-methoxycarbonyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine benzyl ester in 30 ml of piperidine and 120 ml of dichloromethane was stirred for 30 minutes at room temperature. The solvent was removed by evaporation and the residue was chromatographed on silica gel using firstly 20% ethyl acetate in hexane and then 10% methanol in dichloromethane for the elution. Evaporation gave 6.9 g of N-[N-[2-methyl-L-phenyl-alanyl]-3-methyl-L-valyl]-L-leucine benzyl ester in the form of an oil which was used in the next step without further purification.

v) A solution of 6.9 g of the foregoing oil, 2.13 g (13.95 mmol) of 1-hydroxybenzotriazole, 2.68 g (13.95 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 5.93 g (13.95 mmol) of N-[(9-fluorenyl)methoxycarbonyl]-O-tert.-butyl-L-α-glutamic acid in 150 ml of dichloromethane was

stirred at room temperature overnight. The solution was washed with water, sodium hydrogen carbonate solution, 2M hydrochloric acid and saturated sodium chloride solution and dried over anhydrous magnesium sulphate. Evaporation and chromatography of the residue on silica gel using 30% ethyl acetate in petroleum ether (b.p. 40-60°C) for the elution gave 10.89 g of N-[N-[N-[N-[(9-fluorenyl)methoxycarbonyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine benzyl ester as a thick oil. MS: m/e 903 [M+H]+.

vi) A solution of 10.89 g (12.07 mmol) of N-[N-[N-[N-[(9-fluorenyl)methoxycarbonyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine benzyl ester in 30 ml of piperidine and 120 ml of dichloromethane was stirred for 30 minutes at room temperature. The solvent was removed by evaporation and the residue was chromatographed on silica gel using firstly 20% ethyl acetate in hexane and then 10% methanol in dichloromethane for the elution. Evaporation gave N-[N-[N-[O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine benzyl ester in the form of an oil which was used in the next step without further purification.

vii) A solution of the foregoing oil, 4.96 g (12.07 mmol) of N-[(9-fluorenyl)methoxycarbonyl]-O-tert-butyl-L-α-aspartic acid, 1.85 g (12.07 mmol) of 1-hydroxybenzotriazole and 2.32 g (12.07 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride in 100 ml of dichloromethane was stirred at room temperature overnight. The solution was washed with water, sodium hydrogen carbonate solution, 2M hydrochloric acid and saturated sodium chloride solution and dried over anhydrous magnesium sulphate. Evaporation and chromatography of the residue on silica gel using ethyl acetate for the elution gave 10.088 g of N-[N-[N-[N-[N-[(9-fluorenyl)methoxycarbonyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine benzyl ester as a white solid. MS: m/e 1074 [M+H]+.

viii) A solution of 10.088 g (9.4 mmol) of N-[N-[N-[N-[N-[(9-fluorenyl)methoxycarbonyl] O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine benzyl ester in 30 ml of piperidine and 120 ml of dichloromethane was stirred for 30 minutes at room temperature. The solvent was removed by evaporation and the residue was chromatographed on silica gel using firstly 20% ethyl acetate in hexane and then 10% methanol in dichloromethane for the elution. Evaporation gave N-[N-[N-[N-[O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl-2-methyl-L-phenylalanyl]-3-methyl-L-valyl-L-leucine benzyl ester in the form of an oil which was used in the next step without further purification.

ix) A solution of 8 g of the foregoing oil, 1.64 g (9.4 mmol) of tert-butyl hydrogen succinate, 1.44 g (9.4 mmol) of 1-hydroxybenzotriazole and 1.805 g (9.4 mmol) of 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride in dichloromethane was stirred at room temperature overnight. The solution was washed with water, sodium hydrogen carbonate solution, 2M hydrochloric acid and saturated sodium chloride solution and dried over anhydrous magnesium sulphate. Evaporation and trituration of the residue with acetone gave 6.87 g of N-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine benzyl ester as a white solid. MS: m/e 1008.6 $[M+H]^+$, m/e 1030.3 $[M+Na]^+$.

x) A solution of 6.8 g (6.75 mmol) of N-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine benzyl ester in 200 ml of dimethylformamide was hydrogenated over 600 mg of 10% palladium/carbon for 1 hour. The catalyst was removed by filtration and the filtrate was evaporated to give 15 g of crude product which was chromatographed on silica gel using 10-15% methanol in dichloromethane for the elution to give 6 g of N-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-

valyl]-L-leucine as a white solid of melting point 235-236°C; MS: m/e 918.4 [M+H]$^+$, m/e 940.3 [M+Na]$^+$.

xi) 370 mg (2.5 mmol) of N,O-dimethyl 2(S)-(tert-butoxyformamido)butyrohydroxamate were dissolved in 20 ml of anhydrous tetrahydrofuran under nitrogen and the solution was cooled to 0°C in an ice-bath. 1.5 ml (1.5 mmol) of 1M lithium aluminium hydride in tetrahydrofuran were added and the mixture was stirred at 0°C for 10 minutes. 20 ml of saturated aqueous potassium hydrogen sulphate were added and the mixture was stirred vigorously under nitrogen for 30 minutes at room temperature. The mixture was then diluted with 50 ml of diethyl ether and the organic layer was separated, dried over anhydrous magnesium sulphate and the solvent was evaporated. The residue was dissolved in 10 ml of a saturated methanolic hydrogen chloride solution, stirred for 1 hour, then diluted with 50 ml of toluene and evaporated to dryness. The resulting oil was dissolved in 10 ml of dichloromethane and 184 mg (0.2 mmol) of N-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine, 58 mg (0.3 mmol) of 2-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride, 41 mg (0.3 mmol) of 1-hydroxy-7-azabenzotriazole and 350 mg (3.0 mmol) of N-ethylmorpholine were added. The mixture was stirred for 30 minutes then washed in sequence with saturated sodium bicarbonate solution and 2M hydrochloric acid and dried over anhydrous magnesium sulphate. The solution was evaporated to dryness and the residue was chromatographed on silica gel using 4% methanol in dichloromethane for the elution. After trituration with diethyl ether there were obtained 110 mg of N2-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(S)-(dimethoxymethyl)propyl]-leucinamide as a white solid of melting point 242-244°C. MS: m/e 1001.5 [M+H-MeOH]$^+$, m/e 1055 [M+Na]$^+$.

Analysis for $C_{53}H_{88}O_{14}N_6$ [1033.315].
Calculated: C, 61.61; H, 8.58; N, 8.13%
Found: C, 61.52, H, 8.45; N, 8.19%

Example 2

70 mg (0.067 mmol) of N2-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(S)-(dimethoxymethyl)-3-butynyl]-L-leucinamide were stirred in a mixture of 4 ml of trifluoroacetic acid, 4 ml of dichloromethane and 30 mg of water at room temperature for 30 minutes. The solution was evaporated to dryness in a vacuum and the residue was chromatographed on silica gel using dichloromethane/methanol/acetic acid/water (60:13:2:2) for the elution. There were obtained 36 mg of 2(RS)-[[N-[N-[N-[N-[N-[(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4-pentynal (9:1 mixture of diastereoisomers) as a white solid. MS: m/e 829.6 $[M+H]^+$.

The starting material was prepared as follows:

i) A solution of 12.17 g (57.14 mmol) of N-(tert-butoxycarbonyl)-1(S)-amino-4-pentynoic acid, 8.74 g (64.74 mmol) of hydroxybenzotriazole, 6.96 g (71.43 mmol) of N,O-dimethylhydroxylamine, 8.21 g (71.43 mmol) of N-ethylmorpholine and 13.7 g (71.43 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride in 250 ml of dichloromethane was stirred for 18 hours, then washed with 2M hydrochloric acid and saturated sodium bicarbonate solution, dried and evaporated to give 14.2 g of N,O-dimethyl 2(S)-(tert-butoxyformamido)-4-pentynohydroxamate as a viscous gum which slowly crystallized.
Analysis for $C_{12}H_{20}N_2O_4$ [256.302].
Calculated: C, 56.24; H, 7.87; N, 10.93%
Found: C, 56.01, H, 7.81; N, 10.92%

ii) 10 ml (10 mmol) of 1M lithium aluminium hydride in tetrahydrofuran were added to a solution of 3.15 g (12.3 mmol) of N,O-dimethyl 2(S)-(tert-butoxyformamido)-4-pentynohydroxamate in 50 ml of dry tetrahydrofuran at 0°C under a nitrogen

atmosphere. The solution was stirred for 20 minutes and then 40 ml of saturated potassium hydrogen sulphate solution were added dropwise. The mixture was stirred for 15 minutes and then diluted with diethyl ether. The organic layer was dried over magnesium sulphate and evaporated to give an oil which was dissolved in 50 ml of methanolic hydrogen chloride solution. The solution was left at room temperature for 1 hour and then evaporated to dryness to give a dark brown gum. 1.05 g of the gum were added to a solution of 2.06 g (5.84 mmol) of N-[(9-fluorenyl)methoxycarbonyl]-L-leucine, 867 mg (6.42 mmol) of hydroxybenzotriazole, 1.233 g (6.42 mmol) of 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride and 2.216 g (19.27 mmol) of N-ethylmorpholine in 40 ml of dichloromethane. The solution was stirred at room temperature for 18 hours, washed with 2M hydrochloric acid and saturated sodium bicarbonate solution, dried over magnesium sulphate and evaporated to give a gum which was chromatographed on silica gel using ethyl acetate/petrol (2:3) for the elution. There were obtained 1.1 g of N2-[(9-fluorenyl)methoxycarbonyl]-N1-[1(S)-(dimethoxymethyl)-3-butynyl]-L-leucinamide as an off-white solid. ^1H NMR (400 MHz, DMSO-d_6) δ: 0.86 (6H,dd), 1.35-1.65 (3H,m), 2.22-2.39 (2H,m), 2.75(1H,t), 3.22 (3H,s), 3.27 (3H,s), 3.91 (1H,m), 4.08 (1H,m), 4.15-4.3 (4H,m), 7.29 (2H,m), 7.4 (2H,t), 7.42 (lH,d), 7.71 (2H,d), 7.84 (lH,d), 7.88 (2H,d).

iii) 525 mg (1.1 mmol) of N2-[(9-fluorenyl)methoxycarbonyl]-N1-[1(S)-(dimethoxymethyl)-3-butynyl]-L-leucinamide were dissolved in 20 ml of dichloromethane and 5 ml of piperidine and the mixture was stirred at room temperature for 30 minutes. The mixture was evaporated to dryness and the residue was chromatographed on silica gel using firstly ethyl acetate/petrol (1:1) and then methanol/dichloromethane (1:9) for the elution. Evaporation of the dichloromethane solution gave a gum which was added to a solution of 363 mg (1.03 mmol) of N-[(9-fluorenyl)methoxycarbonyl]-3-methyl-L-leucine, 149 mg (1.1 mmol) of hydroxybenzotriazole and 288 mg (1.5 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride in 15 ml of dichloromethane. The mixture was stirred for

18 hours, then washed with 2M hydrochloric acid and saturated sodium bicarbonate solution, dried over magnesium sulphate and evaporated to dryness. The residue was chromatographed on silica gel using ethyl acetate/petrol (1:2) for the elution to give 501 mg of N2-[N-[(9-fluorenyl)methoxycarbonyl]-3-methyl-L-valyl]-N1-[1(S)-(dimethoxymethyl)-3-butynyl]-L-leucinamide as a white foam. MS: m/e 592.3 $[M+H]^+$, 560.3 $[M+H-MeOH]^+$.

iv) 490 mg (0.83 mmol) of N2-[N-[(9-fluorenyl)methoxycarbonyl]-3-methyl-L-valyl]-N1-[1(S)-(dimethoxymethyl)-3-butynyl]-L-leucinamide were dissolved in 16 ml of dichloromethane and 4 ml of piperidine and the mixture was stirred at room temperature for 30 minutes. The mixture was evaporated to dryness and the residue was chromatographed on silica gel using firstly ethyl acetate/petrol (1:1) and then methanol/dichloromethane (1:9) for the elution. Evaporation of the dichloromethane solution gave a gum which was added to a solution of 321 mg (0.8 mmol) of N-[(9-fluorenyl)methoxycarbonyl]-2-methyl-L-phenylalanine, 122 mg (0.9 mmol) of hydroxybenzotriazole and 192 mg (1 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride in 15 ml of dichloromethane. The mixture was stirred for 18 hours, then washed with 2M hydrochloric acid and saturated sodium bicarbonate solution, dried over magnesium sulphate and evaporated to dryness. The residue was chromatographed on silica gel using ethyl acetate/petrol (2:3) for the elution to give a white foam which was dissolved in 16 ml of dichloromethane and 4 ml of piperidine and left at room temperature for 30 minutes. The mixture was evaporated to dryness and the residue was chromatographed on silica gel using firstly ethyl acetate/petrol (1:1) and then methanol/dichloromethane (1:9) for the elution. Evaporation of the dichloromethane solution gave a gum which was added to a solution of 213 mg (0.5 mmol) of N-[(9-fluorenyl)methoxycarbonyl]-O-tert-butyl-L-α-glutamic acid, 74 mg (0.55 mmol) of hydroxybenzotriazole and 115 mg (0.6 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride in 10 ml of dichloromethane. The mixture was stirred for 18 hours, then washed with 2M hydrochloric acid and

saturated sodium bicarbonate, dried over magnesium sulphate and evaporated to dryness. Trituration of the residue with diethyl ether gave 345 mg of N2-[N-[N-[O-tert-butyl-N-[(9-fluorenyl)-methoxycarbonyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(S)-(dimethoxymethyl)-3-butynyl]-leucinamide as a white solid. MS: m/e 938 [M+H]+, 906 [M+H-MeOH]+.

v) 340 mg (0.36 mmol) of N2-[N-[N-[O-tert-butyl-N-[(9-fluorenyl)methoxycarbonyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(S)-(dimethoxymethyl)-3-butynyl]-L-leucinamide were dissolved in 12 ml of dichloromethane and 3 ml of piperidine and the mixture was stirred at room temperature for 30 minutes. The mixture was evaporated to dryness and the residue was chromatographed on silica gel using firstly ethyl acetate/petrol (1:1) and then methanol/dichloromethane (1:9) for the elution. Evaporation of the dichloromethane solution gave a gum which was added to a solution of 144 mg (0.35 mmol) of N-[(9-fluorenyl)methoxy-carbonyl]-O-tert-butyl-L-α-aspartic acid, 54 mg (0.4 mmol) of hydroxybenzotriazole and 96 mg (0.5 mmol) of 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride in 15 ml of dichloromethane. The mixture was stirred for 18 hours, then washed with 2M hydrochloric acid and saturated sodium bicarbonate solution, dried over magnesium sulphate and evaporated to dryness. Trituration of the residue with diethyl ether gave 360 mg of N2-[N-[N-[N-[O-tert-butyl-N-[(9-fluorenyl)methoxycarbonyl]-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(S)-(dimethoxymethyl)-3-butynyl]-L-leucinamide as a white solid. MS: m/e 1077 [M+H-MeOH]+.

vi) 350 mg (0.32 mmol) of N2-[N-[N-[N-[O-tert-butyl-N-[(9-fluorenyl)methoxycarbonyl]-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(S)-(dimethoxymethyl)-3-butynyl]-L-leucinamide were dissolved in 12 ml of dichloromethane and 3 ml of piperidine and the mixture was stirred at room temperature for 30 minutes.

The mixture was evaporated to dryness and the residue was chromatographed on silica gel using firstly ethyl acetate/petrol (1:1) and then methanol/dichloromethane (1:9) for the elution. Evaporation of the dichloromethane solution gave a foam which was added to a solution of 104 mg (0.6 mmol) of succinic acid monotert-butyl ester, 81 mg (0.6 mmol) of hydroxybenzotriazole and 192 mg (1 mmol) of 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride in 10 ml of dichloromethane. The mixture was stirred for 18 hours, then washed with 2M hydrochloric acid and saturated sodium bicarbonate solution, dried over magnesium sulphate and evaporated to dryness. Chromatography of the residue on silica gel using 4% methanol in dichloromethane for the elution and trituration with ethyl acetate gave 145 mg of N2-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(S)-(dimethoxymethyl)-3-butynyl]-L-leucinamide as a white solid. MS: m/e 1043 [M+H]+, 1011 [M+H-MeOH]+.

Example 3

94 mg (0.86 mmol) of N2-[N-[N-[N-[N-[3-(tert-butoxy-carbonyl)-propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[3,3,3-trifluoro-1(S)-(dimethoxymethyl)propyl]-L-leucinamide were stirred in a mixture of 4 ml of trifluoroacetic acid, 4 ml of dichloromethane and 30 mg of water at room temperature for 30 minutes. The solution was evaporated to dryness in a vacuum and the residue was chromatographed on silica gel using dichloromethane/methanol/acetic acid/water (120:15:3:2) for the elution. There were obtained 41 mg of 2(RS)-[[N-[N-[N-[N-[N-(3-carboxy-propionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenyl-alanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyr-aldehyde (7:1 mixture of diastereoisomers) as a white solid. MS: m/e 873 [M+H]+.

The starting material was prepared as follows:

184 mg (0.2 mmol) of N-[N-[N-[N-[N-[3-(tert-butoxy-carbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine were suspended in 6 ml of dichloromethane and treated with 34 mg (0.25 mmol) of hydroxybenzotriazole followed by 391 mg (1.75 mmol) of 3,3,3-trifluoro-1(S)-dimethoxymethyl-propylamine hydrochloride and 690 mg (6 mmol) of N-ethyl-morpholine. The mixture was stirred for 2 hours, then washed in sequence with 2M hydrochloric acid and saturated sodium bicarbonate solution and dried over magnesium sulphate. The solvent was removed by evaporation and the resulting solid, after trituration with diethyl ether, was chromatographed on silica gel using 4% methanol in dichloromethane for the elution. There were obtained 101 mg of N2-[N-[N-[N-[N-[(3-tert-butoxycarbonyl)-O-tert-butyl-L-α-aspartyl-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[3,3,3-trifluoro-1(S)-(dimethoxymethyl)propyl]-L-leucinamide as a white solid. MS: m/e 1088 $[M+H]^+$.

Example 4

0.02 g (0.006 mmol) of 5-[4-[[N-[N-[N-[(9-fluorenyl)-methoxycarbonyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]-N-3,3,3-trifluoro-1(RS)-(dimethoxymethyl)propyl]-amino]methyl]-3,5-dimethoxyphenoxy]-N-(4-methyl-α-(RS)-phenylbenzyl)valeramide-polystyrene conjugate was suspended and agitated in 0.7 ml of dimethylformamide/piperidine (4:1). After 5 minutes the resin was drained and then resuspended in and agitated with 0.7 ml of dimethylformamide/piperidine (4:1) for a further 5 minutes. The resin was then drained and washed five times with 1.5 ml of dimethylformamide.

The resin was then suspended in a solution of 0.026 g (0.06 mmol) of N-[(9-fluorenyl)methoxycarbonyl]-3-(2-naphthyl)-D-alanine in 0.3 ml of dimethylformamide and then a mixture of 0.019 g (0.06 mmol) of 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoraborate and 0.012 g (0.12 mmol) of N-methylmorpholine dissolved in 0.3 ml of

dimethylformamide was added. After agitating for 2 hours the resin was drained and washed five times with 1.5 ml of dimethylformamide.

The resin was resuspended in and agitated with 1.5 ml of dimethylformamide/piperidine (4:1). After 5 minutes the resin was drained and resuspended in and agitated with dimethylformamide/piperidine(4:1) for a further 5 minutes. Then, the resin was drained and washed five times with 1.5 ml of dimethylformamide.

The resin was then suspended in a solution of 0.025 g (0.06 mmol) of N-[(9-fluorenyl)methoxycarbonyl]-O-tert-butyl-L-α-aspartic acid in 0.3 ml of dimethylformamide and then a mixture of 0.019 g (0.06 mmol) of 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoraborate and 0.012 g (0.12 mmol) of N-methylmorpholine dissolved in 0.3 ml of dimethylformamide was added. After agitating for 2 hours the resin was drained and washed five times with 1.5 ml of dimethylformamide.

The resin was resuspended in and agitated with 1.5 ml of dimethylformamide/piperidine (4:1). After 5 minutes the resin was drained and resuspended in and agitated with dimethylformamide/piperidine (4:1) for a further 5 minutes. Then, the resin was drained and washed five times with 1.5 ml of dimethylformamide.

The resin was then suspended in a solution of 0.01 g (0.06 mmol) tert-butyl hydrogen succinate in 0.3 ml of dimethylformamide and treated with a mixture of 0.019 g (0.06 mmol) 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate and 0.012 g (0.12 mmol) of N-methylmorpholine dissolved in 0.3 ml of dimethylformamide. After agitating for 2 hours the resin was drained and washed 5 times with 1.5 ml of dimethylformamide and then twice with 1.5 ml of dichloromethane.

The resin was treated with 0.8 ml of trifluoroacetic acid/water (19:1) and then agitated for 30 minutes. It was then filtered off and washed with 0.8 ml of trifluoroacetic acid/ water (19:1). The combined trifluoroacetic acid/water mixtures were then evaporated in a vacuum centrifuge and the residue was suspended in 0.8 ml of acetonitrile/water (1:1) and freeze dried. There were obtained 6.3 mg of 2(RS)-[[N-[N-[N-[N-[N-(3-carboxy-propionyl)-L-α-aspartyl]-3-(2-naphthyl)-D-alanyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde as a white solid; MS: m/e 941.5 $[M+H]^+$.

The starting material was prepared as follows:

i) 18 g (60.0 mmol) of N,O-dimethyl 2(RS)-(tert-butoxyformamido)-4,4,4-trifluorobutyrohydroxamate were dissolved in 230 ml of anhydrous tetrahydrofuran and the solution was cooled to 0°C. 48 ml (48 mmol) of a 1M solution of lithium aluminium hydride in tetrahydrofuran were then added dropwise while maintaining the temperature at 0°C. The mixture was stirred for 10 minutes at 0°C and then the reaction was quenched by the dropwise addition of saturated potassium hydrogen sulphate solution to pH 1 while maintaining the temperature at below 20°C. The resulting white slurry was stirred vigorously for a further 30 minutes and was then partitioned in three equal aliquots of diethyl ether. The combined diethyl ether fractions were washed with saturated sodium chloride solution, dried over anhydrous magnesium sulphate, filtered and evaporated. The residue was then dissolved in 100 ml of anhydrous saturated methanolic hydrogen chloride solution and left overnight at 4°C. The mixture was evaporated and the residue was triturated with dichloromethane. The filtrate was evaporated and the residue was chromatographed on silica gel using 5% methanol, 3% acetic acid and 1.5% water in dichloromethane for the elution. There were obtained 8.80 g of 3,3,3-trifluoro-2(RS)-(dimethoxymethyl)-propylamine hydrochloride as a white solid. ^1H NMR : $(CDCl_3)\delta$: 2.60-2.96 (m,2H), 3.49 (d,6H), 3.57-3.69 (q,1H), 4.66 (d,1H), 8.72 (br s,3H).

ii) To a stirred mixture of 5.6 g (25.0 mmol) of 3,3,3-trifluoro-2(RS)-(dimethoxymethyl)-propylamine hydrochloride 3.65 ml of triethylamine, 7.8 g (25.0 mmol) of 4-[4-(ethoxy-carbonyl)butoxy]2,6-dimethoxybenzaldehyde and 25 g of 3Å molecular sieves in dichloromethane were added 5.8 g (27.5 mmol) of sodium triacetoxyborohydride. After 3 hours the molecular sieves were removed by filtration. The filtrate was then washed with three equal aliquots of saturated sodium bicarbonate solution and dried over anhydrous magnesium sulphate and filtered. The solvent was removed by evaporation and the resulting orange oil was chromatographed on silica gel using 60% ethyl acetate in hexane for the elution. There were obtained 10.4 g of ethyl 5-[4-[[3,3,3-trifluoro-1(RS)-(dimethoxymethyl)propylamino]methyl]-3,5-dimethoxyphenoxy]-valerate as a pale orange oil; ^1H NMR : $(CDCl_3)\delta$: 1.25 (t,3H), 1.78-1.87 (m,4H), 2.18-2.52 (m,4H), 2.86-2.92 (m,1H), 3.33 (d,6H), 3.77 (s,6H), 3.81 (d,2H), 3.96 (t,2H), 4.13 (q,2H), 4.26 (d,1H), 6.18 (s,2H); MS: m/e 482.2 [M+H], 504.2 [M+Na].

iii) A solution of 6.6 g (18.7 mmol) of N-[(9-fluorenyl)-methoxycarbonyl]-L-leucine and 9.7 g (18.7 mmol) of 7-azabenzotriazol-1-yloxytris(pyrrolidino)phosphonium hexa-fluorophosphate in 50 ml of anhydrous dichloromethane was stirred at room temperature for 15 minutes. To this mixture were then added 6.0 g (12.4 mmol) of ethyl 5-[4-[[3,3,3-trifluoro-1(RS)-(dimethoxymethyl)propylamino]methyl]-3,5-dimethoxyphenoxy]valerate and 4.3 ml of (24.8 mmol) diiso-propylethylamine. After stirring overnight at 25°C the mixture was diluted with dichloromethane and washed in sequence with water, 10% citric acid solution, saturated sodium hydrogen carbonate solution and saturated sodium chloride solution, then dried over anhydrous magnesium sulphate and filtered. The solvent was removed by evaporation and the residue was chromatographed on silica gel using 30% ethyl acetate in hexane for the elution. There were obtained 8.06 g of ethyl 5-[4-[[N-[N-[(9-fluorenyl)methoxycarbonyl]-L-leucyl]-N-[3,3,3-trifluoro-1(RS)-(dimethoxymethyl)propyl]amino]methyl]-3,5-dimethoxy-phenoxy]valerate; MS: m/e 839.4 [M+Na], 855.3 [M+K].

iv) 8.0 g (9.8 mmol) of 5-[4-[[N-[N-[(9-fluorenyl)methoxycarbonyl]-L-leucyl]-N-[3,3,3-trifluoro-1(RS)-(dimethoxymethyl)-propyl]amino]methyl]-3,5-dimethoxyphenoxy]valerate and 40 ml of piperidine were dissolved in 145 ml of dry dichloromethane and the solution was stirred at room temperature for 30 minutes. It was then evaporated in a vacuum and the residue was chromatographed on silica gel using 2% methanol, 49% dichloromethane and 49% hexane followed by 5% methanol, 47.5% dichloromethane and 47.5% hexane for the elution. There were obtained 4.09 g of ethyl 5-[4-[[N-[3,3,3-trifluoro-1(RS)-dimethoxymethyl)propyl]-N-(L-leucyl)amino]methyl]-3,5-dimethoxyphenoxy]valerate as a clear stiff oil; MS: m/e 595 [M+H].

v) A solution of 2.76 g (7.8 mmol) of N-[(9-fluorenyl)-methoxycarbonyl]-3-methyl-L-valine, 1.60 g (8.5 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1.60 g (10.7 mmol) of N-hydroxybenzotriazole in 70 ml of dichloromethane was stirred at 0°C for 15 minutes. There were then added 4.06 g (7.1 mmol) of ethyl 5-[4-[[N-[3,3,3-trifluoro-1(RS)-(dimethoxymethyl)propyl]-N-(L-leucyl)-amino]methyl]-3,5-dimethoxyphenoxy]valerate and 2.7 ml (21.3 mmol) of N-ethylmorpholine in 70 ml of dichloromethane. After stirring overnight at room temperature the mixture was washed in sequence with 10% citric acid solution, saturated sodium hydrogen carbonate solution and saturated sodium chloride solution, dried over anhydrous magnesium sulphate, filtered and evaporated. The residue was chromatographed on silica gel using 35% ethyl acetate in hexane for the elution. There were obtained 6.11 g of ethyl 5-[4-[[N-[N-[N-[(9-fluorenyl)methoxycarbonyl]-3-methyl-L-valyl]-L-leucyl]-N-[3,3,3-trifluoro-1(RS)-(dimethoxyethyl)-propyl]amino]methyl]-3,5-dimethoxy-phenoxy]valerate as a white foam; MS: m/e 952.5 [M+Na], 968.5 [M+K].

vi) 5.8 g (6.3 mmol) of ethyl 5-[4-[[N-[N-[N-[(9-fluorenyl)-methoxycarbonyl]-3-methyl-L-valyl]-L-leucyl]-N-[3,3,3-trifluoro-1(RS)-(dimethoxyethyl)propyl]amino]methyl]-3,5-dimethoxy-phenoxy]valerate and 18 ml of piperidine were

dissolved in 90 ml of dichloromethane and the solution was stirred at room temperature for 1 hour. It was then evaporated and the residue was chromatographed on silica gel using 3% methanol, 48.5% dichloromethane and 48.5% hexane for the elution. There were obtained 4.1 g of ethyl 5-[4-[[N-[3,3,3-trifluoro-1(RS)-(dimethoxymethyl)propyl]-N-[N-(3-methyl-L-valyl)-L-leucyl]amino]methyl]-3,5-dimethoxyphenoxy]-valerate as a white foam; MS: m/e 708.6 [M+H], 730.5 [M+Na].

vii) 4.0 g (5.7 mmol) of ethyl 5-[4-[[N-[3,3,3-trifluoro-1(RS)-(dimethoxymethyl)propyl]-N-[N-(3-methyl-L-valyl)-L-leucyl]-amino]methyl]-3,5-dimethoxyphenoxy]-valerate were dissolved in 40 ml of methanol. 2.4 g (17.3 mmol) of potassium carbonate and 8.0 ml of water were then added and the mixture was stirred for 2 days at room temperature. The solvent was removed by evaporation and the residue was dissolved in 20 ml of water and 20 ml of dioxan. 2.9 g (8.6 mmol) of N-[(9-fluorenyl)-methoxy-carbonyloxy]-succinimide were then added and the mixture was stirred for 3 hours. The mixture was adjusted to pH 3 with 10% citric acid and then washed with three equal aliquots of dichloromethane. The combined organic layers were washed with saturated sodium chloride solution, dried over anhydrous magnesium sulphate, filtered and the filtrate was evaporated. The residue was chromatographed on silica gel using 4% tert-butyl methyl ether in dichloromethane for the elution. There were obtained 5.12 g of 5-[4-[[N-[N-[N-[(9-fluorenyl)methoxy-carbonyl]-3-methyl-L-valyl]-L-leucyl]-N-[3,3,3-trifluoro-1(RS)-(dimethoxymethyl)propyl]amino]methyl]-3,5-dimethoxyphenoxy]-valeric acid as a white foam; MS: m/e 870.8 [M+H-MeOH], 888.7 [M+H-CH_3], 889.7 [M-CH_3] 902.7 [M+H], 924.7 [M+Na].

viii) 5.4 g (5.4 mmol) of 4-methylbenzhydrylamine resin were swollen in 30 ml of dimethylformamide, excess solvent was drained from the resin and it was then washed twice with 20 ml dimethylformamide/N-methylmorpholine (9:1). The resin was then resuspended in 10 ml of dimethylformamide containing 4.98 g (5.4 mmol) of 5-[4-[[N-[N-[N-[(9-fluorenyl)methoxy-carbonyl]-3-methyl-L-valyl]-L-leucyl]-N-[3,3,3-trifluoro-1(RS)-

dimethoxymethyl)propyl]amino]methyl-3,5-dimethoxyphenoxy]-valeric acid and 1.74 g (5.4 mmol) of 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoraborate. Thereto there were added 1.18 ml (10.8 mmol) of N-methylmorpholine dissolved in 10 ml of dimethylformamide. The resulting mixture was agitated for 2 hours and the resin was then drained and washed five times with 30 ml of dimethylformamide. The resin was then resuspended in 30 ml of dimethylformamide containing 2.03 ml (21.6 mmol) of acetic anhydride and 2.96 ml (27 mmol) of N-methylmorpholine. This mixture was agitated for 30 minutes and the resin was then drained and washed five times with 30 ml of dimethylformamide each time. The resin was resuspended in and agitated in 30 ml of dimethylformamide/piperidine (4:1). After 5 minutes the resin was drained, resuspended and again agitated in the foregoing dimethylformamide/piperidine mixture for a further 5 minutes. The resin was then drained and washed five times with 30 ml of dimethylformamide.

ix) A solution of 3.2 g (8.1 mmol) of N-[(9-fluorenyl)methoxycarbonyl]-3-(2-methylphenyl)-L-alanine and 2.17 g (6.75 mmol) of 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate in 22 ml of dimethylformamide was added to the resin from paragraph viii) and subsequently 1.5 ml (13.5 mmol) of N-methylmorpholine were added. The mixture was agitated for 30 minutes and then the resin was drained and washed five times with 30 ml of dimethylformamide, twice with 30 ml of dichloromethane, twice with 30 ml of ethyl acetate and twice with 30 ml of diethyl ether. After drying there were obtained 8.95 g of 5-[4-[[N-[N-[N-[(9-fluorenyl)methoxycarbonyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]-N-[3,3,3-trifluoro-1(RS)-(dimethoxymethyl)propyl]amino]methyl]-3,5-dimethoxyphenoxy]-N-(4-methyl-α-(RS)-phenylbenzyl)-valeramide-polystyrene conjugate as a pale brown solid (0.31 mmol/g loading estimated by quantitation of dibenzofulvene at 301 nm).

Example 5

0.236 g (0.215 mmol) of N2-[N-[N-[N-[N-[3-(tert-butoxy-carbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(RS)-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-butenyl]-L-leucinamide was dissolved in 1.5 ml of water, 13.5 ml of trifluoroacetic acid and 7 ml of dichloromethane and the solution was stirred at room temperature for 1 hour and then left to stand at 4°C for 18 hours. The solution was then diluted with toluene and evaporated. The residue was triturated with diethyl ether and the resulting solid was filtered off. The solid was purified by RP-HPLC on a Dynamax C18 column (5 micron, 300Å, 21.4 mm x 50 mm). The elution gradient comprised 95% SSA:5% SSB to 95%:SSB 5% SSA over 6 minutes and there were obtained, after lyophilization, 69 mg of 1(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-3-butenyl-boronic acid as a foam; MS: m/e 847 [M+H].

The starting material was prepared as follows:

i) 2 g (9.48 mmol) of 2-(dichloromethyl)-4,4,5,5-tetra-methyl-1,3,2-dioxaborolane were dissolved in 30 ml of tetra-hydrofuran and the solution was cooled under a nitrogen atmos-phere to -78°C. 9.5 ml (9.5 mmol) of 1M allylmagnesium bromide were added dropwise and the solution was stirred at room temperature for 18 hours. The solution was partitioned between ethyl acetate, saturated sodium chloride solution and 2M hydro-chloric acid solution. The aqueous layer was extracted with ethyl acetate and the organic layers were combined and dried over anhydrous sodium sulphate. After filtration and evaporation the oil obtained was distilled to give 1.45 g of 2-(1(RS)-chloro-3-butenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane; b.p. 53°C/0.4 mm Hg.

ii) 6.6 ml (6.6 mmol) of 1M lithium bis(trimethylsilyl)amide in tetrahydrofuran were added dropwise to a solution of 1.43 g

(6.6 mmol) of 2-(1(RS)-chloro-3-butenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in 20 ml of tetrahydrofuran under nitrogen at -78°C. The solution was then stirred overnight at room temperature. The solvent was removed by evaporation and the residue was taken up in diethyl ether. Insoluble material was removed by filtration and the filtrate was cooled to 0°C. 1.5 ml (19.8 mmol) of trifluoroacetic acid were added and the solution was stirred at 0°C for 30 minutes. The resulting precipitate was filtered off and dried to give 0.5 g of α-(RS)-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-methylamine trifluoroacetate which was used in the next step without further purification.

iii) 0.25 g (0.27 mmol) of N-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine was dissolved in 4 ml of dimethylformamide and 4 ml of dichloromethane. 0.15 ml (1.6 mmol) of N-methylmorpholine was added and the solution was cooled to -15°C under a nitrogen atmosphere. 50 mg (0.38 mmol) of isobutyl chloroformate were added and the solution was stirred for 10 minutes at -15°C. 0.1 g (0.32 mmol) of α-(RS)-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-methylamine trifluoroacetate was added and the mixture was stirred at room temperature for 18 hours. After evaporation the residue was partitioned between ethyl acetate and 2M hydrochloric acid. The organic layer was washed with 2M hydrochloric acid, water and saturated sodium chloride solution and then dried over anhydrous sodium sulphate. After evaporation there was obtained 0.3 g of N2-N-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(RS)-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-butenyl]-L-leucinamide in the form of a solid; MS: m/e 1097 [M+H].

Example 6

0.25 g (0.23 mmol) of N2-N-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(RS)-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl]-L-leucinamide was dissolved in 1.5 ml of water, 13.5 ml of trifluoroacetic acid and 7 ml of dichloromethane and the solution was stirred at room temperature for 1 hour and then left to stand at 4°C for 18 hours. The solution was diluted with toluene and evaporated. The residue was triturated with diethyl ether and the resulting solid was filtered off. The solid was purified by RP-HPLC on an Aquapore octyl column (20 micron, 100 mm x 10 mm). The elution gradient comprised 95% SSA:5% SSB to 5% SSA:95% SSB over 6 minutes and there were obtained, after lyophilization, 92 mg of 1(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]propylboronic acid as a foam; MS: m/e 835 [M+H].

The starting material was prepared as follows:

i) 2.64 g (12.5 mmol) of 2-(dichloromethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane were dissolved in 30 ml of tetrahydrofuran and the solution was cooled under a nitrogen atmosphere to -78°C. 11.8 ml (12.5 mmol) of 1.06M ethylmagnesium bromide were added dropwise and the solution was stirred at room temperature for 18 hours. The solution was partitioned between ethyl acetate, saturated sodium chloride solution and 2M hydrochloric acid solution. The aqueous layer was extracted with ethyl acetate and the organic layers were combined and dried over anhydrous sodium sulphate. After filtration and evaporation the oil obtained was distilled to give 2.04 g of 2-[1(RS)-chloropropyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane; b.p. 53°C/0.8 mm Hg.

ii) 10 ml (10 mmol) of 1M lithium bis(trimethylsilyl)amide in tetrahydrofuran were added dropwise to a solution of 2.03 g

(9.9 mmol) of 2-[1(RS)-chloropropyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in 20 ml tetrahydrofuran under a nitrogen atmosphere at -78°C. The solution was then stirred overnight at room temperature. The solvent was removed by evaporation and the residue was taken up in diethyl ether. Insoluble material was removed by filtration and the filtrate was cooled to 0°C. 2.3 ml (30 mmol) of trifluoroacetic acid were added and the solution was stirred at 0°C for 30 minutes. The resulting precipitate was filtered off and dried to give 0.5 g of α-(RS)-ethyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-methylamine trifluoroacetate as a white solid.

Analysis for $C_{11}H_{21}BNF_3O_4$ [299.15].

Calculated: C, 44.17; H, 7.08; N, 4.68%

Found: C, 44.06, H, 7.05, N, 4.71%.

iii) 0.25 g (0.27 mmol) of N-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine was dissolved in 2 ml of dimethylformamide and 5 ml of dichloromethane. 0.15 ml (1.6 mmol) of N-methylmorpholine was added and the solution was cooled to -15°C under a nitrogen atmosphere. 50 mg (0.38 mmol) of isobutyl chloroformate were added and the solution was stirred for 10 minutes at -15°C. 0.1 g (0.33 mmol) of α-(RS)-ethyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-methylamine trifluoroacetate was added and the mixture was stirred at room temperature for 18 hours. After evaporation the residue was partitioned between ethyl acetate and 2M hydrochloric acid. The organic layer was washed with 2M hydrochloric acid, water and saturated sodium chloride solution and then dried over anhydrous sodium sulphate. After evaporation there was obtained 0.26 g of N2-N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(RS)-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl]-L-leucinamide in the form of a solid; MS: m/e 1085 [M+H].

Example 7

0.16 g (14.6 mmol) of N2-[N-[N-[N-[N-[3-(tert-butoxy-carbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(RS)-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl]-L-leucinamide was dissolved in 4 ml of trifluoroacetate acid and 4 ml of dichloromethane. 4 drops of water were added and the solution was stirred at room temperature for 3 hours. The residue was triturated with diethyl ether and the resulting solid was filtered off and dried to give, after lyophilization, 139 mg of 1(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]butylboronic acid as a foam; MS: m/e 849 [M+H].

The starting material was prepared as follows:

i) 0.5 g (2.37 mmol) of 2-(dichloromethyl)-4,4,5,5-tetra-methyl-1,3,2-dioxaborolane was dissolved in 10 ml of tetra-hydrofuran and the solution was cooled under a nitrogen atmos-phere to -78°C. 2.4 ml (2.4 mmol) of 1M propylmagnesium bromide were added dropwise and the solution was stirred at room temperature for 18 hours. The solution was partitioned between ethyl acetate, saturated sodium chloride solution and 2M hydrochloric acid solution. The aqueous layer was extracted with ethyl acetate and the organic layers were combined and dried over anhydrous sodium sulphate. After evaporation there was obtained 0.38 g of 2-[1(RS)-chlorobutyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as an oil which was used in the next step without further purification.

ii) 1.7 ml (1.7 mmol) of 1M lithium bis(trimethylsilyl)amide in tetrahydrofuran were added dropwise to a solution of 0.37 g (1.69 mmol) of 2-[1(RS)-chlorobutyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane in 20 ml of tetrahydrofuran under nitrogen at -78°C. The solution was then stirred overnight at room temper-ature. The solvent was removed by evaporation and the residue was taken up in diethyl ether. Insoluble material was removed by

filtration and the filtrate was cooled to 0°C. 0.39 ml (5.1 mmol) of trifluoroacetic acid was added and the solution was stirred at 0°C for 30 minutes. The solution was evaporated and the residue was co-evaporated with toluene to give 0.62 g of α-(RS)-propyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-methylamine trifluoroacetate as a brown oil which was used in the next step without further purification.

iii) 0.2 g (0.218 mmol) of N-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine was dissolved in 2 ml of dimethylformamide and 6 ml of dichloromethane. 0.12 ml (1.1 mmol) of N-methylmorpholine was added and the solution was cooled to -15°C under a nitrogen atmosphere. 40 mg (0.31 mmol) of isobutyl chloroformate were added and the solution was stirred for 10 minutes at -15°C. 0.14 g (0.44 mmol) of α-(RS)-propyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-methylamine trifluoroacetate was added and the mixture was stirred at room temperature for 66 hours. After evaporation the residue was partitioned between ethyl acetate and 2M hydrochloric acid. The organic layer was washed with 2M hydrochloric acid, water and saturated sodium chloride solution and then dried over anhydrous sodium sulphate. After evaporation there was obtained 0.17 g of N2-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(RS)-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl]-L-leucinamide in the form of a solid; NMR (DMSO, 400 MHz) δ: 0.75-0.9 (m,17H), 1.01-1.08 (m,6H), 1.15-1.25 (m,1H), 1.35 9s,36H), 1.4-1.7 (m,4H), 1.75-1.8 (m,1H), 2.05-2.15 (m,2H), 2.23 (s,3H), 2.29-2.41 (m,6H), 2.55-2.6 (m,1H), 2.7-2.74 (m,1H), 2.95-3.05 (m,1H), 4.15-4.25 (m,3H), 4.48-4.55 (m,1H), 4.6-4.7 (m,1H), 7.05-7.11 (m,4H), 7.7-7.81 (m,2H), 8.05-8.12 (m,2H), 8.15-8.25 (m,2H).

Example 8

0.126 g (0.116 mmol) of N2-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-

α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1[3,3-difluoro-[1(S)-(dimethoxymethyl)-butyl]-L-leucinamide was dissolved in 5 ml of trifluoroacetic acid and 5 ml of dichloromethane. A few drops of water were added and the solution was stirred at room temperature for 1 hour. The residue was evaporated, the residue was triturated with diethyl ether and the resulting solid was filtered off. The solid was purified by chromatography on silica gel using dichloromethane/methanol/acetic acid/water (75:15:3:2) for the elution. There were obtained 67 mg of 2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4-difluorovaleraldehyde as a cream colouredsolid of melting point 128-130°C.

The starting material was prepared as follows:

i) 1.5 g (4.62 mmol) of 4,4-difluoro-L-norvaline p-toluenesulphonate were dissolved in dimethylformamide. 1.71 g (7.85 mmol) of di-tert-butyl dicarbonate and 3.23 ml (23.25 mmol) of triethylamine were added and the solution was stirred at 60°C for 3 hours. The solution was evaporated and the residue was partitioned between ethyl acetate and 2M hydrochloric acid. The organic layer was dried over anhydrous sodium sulphate and evaporated. The resulting oil was purified by chromatography on silica gel using ethyl acetate for the elution. There were obtained 1.16 g of N-(tert-butoxycarbonyl)-4,4-difluoro-L-norvaline as an orange oil which was used directly in the next step.

ii) 1.16 g (4.62 mmol) of N-(tert-butoxycarbonyl)-4,4-difluoro-L-norvaline were dissolved in 30 ml of dichloromethane. 6.4 ml (46.2 mmol) of triethylamine, 564 mg (4.62 mmol) of N,N-dimethylaminopyridine, 1.77 g (9.24 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 1.8 g (18.5 mmol) of N,O-dimethylhydroxylamine hydrochloride were added and the solution was stirred at room temperature for 18 hours. The mixture was diluted with ethyl acetate, washed with 2M hydrochloric acid and aqueous sodium hydrogen carbonate

solution, dried over anhydrous sodium sulphate and evaporated to give an oil which was purified by chromatography on silica gel using ethyl acetate for the elution. There were obtained 547 mg of N,O-dimethyl 2(S)-(tert-butoxyformamido)-4,4-difluoro-valerohydroxamate as a colourless oil; MS: m/e 297 [M+H].

iii) 547 mg (1.85 mmol) of N,O-dimethyl 2(S)-(tert-butoxy-formamido)-4,4-difluorovalerohydroxamate were dissolved in 12 ml of tetrahydrofuran and the solution was stirred at 0°C. 1.76 ml (1.76 mmol) of 1M lithium aluminium hydride in tetrahydrofuran were added and the solution was stirred for 15 minutes. The mixture was partitioned between ethyl acetate and saturated aqueous potassium hydrogen sulphate solution. The organic layer was evaporated and the residue was dissolved in freshly prepared methanolic hydrogen chloride solution. After 1 hour the solution was evaporated to give 372 mg of 3,3-difluoro-1(S)-(dimethoxymethyl)butylamine hydrochloride as a white solid; MS: m/e 184 [M+H].

iv) 0.3 g (0.33 mmol) of N-[N-[N-[N-[N-[3-(tert-butoxy-carbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine was dissolved in 15 ml of dichloromethane. 0.22 ml (1.98 mmol) of N-methylmorpholine, 96 mg (0.5 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 45 mg (0.33 mmol) of hydroxybenzotriazole and 217 mg (0.99 mmol) of 3,3-difluoro-1(S)-(dimethoxymethyl)butylamine hydrochloride were added and the solution was stirred at room temperature for 18 hours. The mixture was washed with 2M hydrochloric acid and aqueous sodium hydrogen carbonate solution, dried over anhydrous sodium sulphate and evaporated. The residue was triturated with diethyl ether and the resulting solid was filtered off and dried. There were obtained 143 g of N2-[N-[N-[N-[N-[3-(tert-butoxy-carbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[3,3-difluoro-1(S)-dimethoxymethyl)butyl]-L-leucinamide; MS: m/e 1106 $[M+Na]^+$.

Example 9

80 mg (0.075 mmol) of N2-[N-[N-[N-[N-[3-(tert-butoxy-carbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(R)-dimethoxymethyl)-2-(methylthio)ethyl]-L-leucinamide were dissolved in 10 ml of trifluoroacetic acid/dichloromethane (1:1) containing 3 drops of water and the solution was stirred for 90 minutes under a nitrogen atmosphere. The solution was evaporated to dryness under a vacuum and the residue was re-evaporated twice with toluene. The solid was triturated with 10 ml of diethyl ether to give 60 mg of 2(R)-[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-3-(methylthio)-propionaldehyde as a white solid; MS: m/e 851.5 $[M+H]^+$.

The starting material was prepared as follows:

i) 2 g (8.51 mmol) of N-(tert-butoxycarbonyl)-S-methyl-L-cysteine were dissolved in 60 ml of anhydrous tetrahydrofuran and then 1.81 g (11.9 mmol) of 1-hydroxybenzotriazole hydrate, 2.28 g (11.88 mmol) of 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride, 1.16 g (11.90 mmol) of N,O-dimethylhydroxylamine hydrochloride and 5.9 ml (33.87 mmol) of N,N-diisopropylethylamine were added. The mixture was stirred overnight at room temperature. The solvent was removed by evaporation and the residue was partitioned between ethyl acetate and 5% (w/v) aqueous citric acid. The organic phase was washed with saturated aqueous sodium bicarbonate solution and then with saturated sodium chloride solution, dried over magnesium sulphate and evaporated under a vacuum to give 2.27 g of N,O-dimethyl 2(R)-(tert-butoxyformamido)-3-(methyl-thio)propionohydroxamate as a colourless oil; MS: m/e 279 $[M+H]^+$.

ii) 2.22 g (7.90 mmol) of N,O-dimethyl 2(R)-(tert-butoxy-formamido)-3-(methylthio)propionohydroxamate were dissolved in 25 ml of anhydrous tetrahydrofuran and the solution was

cooled to 0°C. 4.69 ml (4.69 mmol) of a 1M solution of lithium aluminium hydride in tetrahydrofuran were added dropwise and the mixture was stirred for 15 minutes. The reaction was quenched by the dropwise addition of saturated aqueous potassium hydrogen sulphate solution and then 50 ml of diethyl ether were added. The mixture was stirred vigorously for 20 minutes. The organic phase was separated, washed with saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate and evaporated to give 1.75 g of aldehyde which, without further purification, was dissolved in 20 ml of saturated methanolic hydrogen chloride solution and stirred for 2 hours under a nitrogen atmosphere at room temperature. The solvent was removed by evaporation and the residue was re-evaporated twice with toluene to give 1.3 g of dimethyl acetal as a colourless oil.

90 mg (0.45 mmol) of the dimethyl acetal were dissolved in 40 ml dichloromethane and then 200 mg (0.22 mmol) of N-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine, 100 mg (0.87 mmol) of N-ethylmorpholine, 40 mg (0.26 mmol) of 1-hydroxybenzotriazole hydrate and 50 mg (0.26 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added. The solution was stirred overnight at room temperature. The organic phase was washed with 5% (w/v) aqueous citric acid and then with saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate and evaporated under a vacuum. The resulting oil was triturated with 10 ml of diethyl ether to give 165 mg of N2-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(R)-(dimethoxymethyl)-2-(methylthio)ethyl]-L-leucinamide as a white solid; MS: m/e 1065.7 $[M+H]^+$.

Example 10

50 mg (0.048 mmol) of N2-[N-[N-[N-[N-[3-(tert-butoxy-carbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(S)-(dimethoxymethyl)-3-butenyl]-L-leucinamide were dissolved in 4 ml of trifluoroacetic acid/dichloromethane (1:1) containing 3 drops of water and the solution was stirred for 1 hour under nitrogen. The solution was evaporated to dryness under a vacuum and the residue was re-evaporated twice with toluene. The solid was triturated with 10 ml of diethyl ether to give 30 mg of 2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4-pentenaldehyde; MS: m/e 831.5 $[M+H]^+$.

The starting material was prepared as follows:

i) 1.13 g (7.46 mmol) of L-allylglycine hydrochloride were dissolved in 20 ml of saturated aqueous sodium bicarbonate solution and 20 ml of dioxan. 1.95 g (8.93 mmol) of di-tert-butyl dicarbonate were added and the solution was stirred overnight and then evaporated to dryness under a vacuum. The residue was partitioned between diethyl ether and water. The aqueous phase was acidified with 2M hydrochloric acid and extracted with ethyl acetate. The organic phase was dried over magnesium sulphate and evaporated under a vacuum to give 1.6 g of N-(tert-butoxycarbonyl)-L-allylglycine as a colourless oil. ^1H NMR (250 MHz, $CDCl_3$) δ: 1.4 (s,9H), 2.4-2.7 (m,2H), 4.3-4.5 (m,1H), 5.0 (br.d,1H), 5.1-5.2 (m,2H), 5.6-5.8 (m,1H)

ii) N,O-Dimethyl 2(S)-(tert-butoxyformamido)-4-penteno-hydroxamate was obtained in a manner analogous to that described in Example 10 i) from 1.6 g (7.44 mmol) of N-(tert-butoxycarbonyl)-L-allylglycine, 1.4 g (10.4 mmol) of 1-hydroxy-benzotriazole, 1.99 g (10.4 mmol) of 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride, 1.02 g (10.46 mmol) of N,O-dimethylhydroxylamine hydrochloride and 2.6 ml (14.93 mmol) of ethyl diisopropylamine. This gave 1.9 g of

product as a colourless oil. ^1H NMR (250 MHz, $CDCl_3$) δ: 1.4 (s,9H), 2.3-2.6 (m,2H), 3.2 (s,3H), 3.8 (s,3H), 4.6-4.7 (m,1H), 5.0-5.4 (m,3H), 5.6-5.8 (m,1H).

iii) 1.9 g (7.36 mmol) of N,O-dimethyl 2(S)-(tert-butoxyformamido)-4-pentenohydroxamate were dissolved in 20 ml of anhydrous tetrahydrofuran and the solution was cooled to 0°C. 5.40 ml (5.4 mmol) of a 1M solution of lithium aluminium hydride in tetrahydrofuran were added dropwise and the mixture was stirred for 25 minutes. The reaction was quenched by the dropwise addition of saturated aqueous potassium hydrogen sulphate and then 50 ml of diethyl ether were added. The mixture was stirred vigourously for 20 minutes. The organic phase was separated, washed with saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate and evaporated to give the aldehyde which, without further purification, was dissolved in 25 ml of saturated methanolic hydrogen chloride solution and stirred for 2 hours at room temperature. The solvent was removed by evaporation and the residue was re-evaporated twice with toluene to give the amino acid acetal as a brown oil.

iv) 40 mg (0.22 mmol) of the amino acid acetal were dissolved in 4 ml of dichloromethane and then 200 mg (0.22 mmol) of N-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine, 0.1 ml (0.78 mmol) of N-ethylmorpholine, 35 mg (0.22 mmol) of 1-hydroxybenzotriazole monohydrate and 50 mg (0.26 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added. The solution was stirred overnight at room temperature. The organic phase was washed with 5% (w/v) aqueous citric acid solution and then with saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate and evaporated under a vacuum. The resulting oil was triturated with 10 ml of diethyl ether to give 148 mg of N2-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(S)-(dimethoxymethyl)-

3-butenyl]-L-leucinamide as a white solid; MS: m/e 1013.6 [M+H-MeOH]+.

Example 11

90 mg (0.081 mmol) of N2-[N-[N-[N-[N-[3-(tert-butoxy-carbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[2-(butylthio)-1(R)-(dimethoxymethyl)ethyl]-L-leucinamide were dissolved in 10 ml of trifluoroacetic acid/dichloromethane (1:1) containing 3 drops of water and the solution was stirred for 90 minutes under nitrogen. The solution was evaporated to dryness under a vacuum and the residue was re-evaporated twice with toluene. The solid was triturated with 10 ml of diethyl ether to give 80 mg of 2(R)-[[N-[N-[N-[N-[N-(3-carboxy-propionyl)-L-α-aspartyl-L-α-glutamyl]-2-methyl-L-phenyl-alanyl]-3-methyl-L-valyl]-L-leucyl]amino]-3-(butylthio)propion-aldehyde as a white solid. MS: m/e 893.4 [M+H]+.

The starting material was prepared as follows:

i) 2 g (16.53 mmol) of L-cysteine were dissolved in 40 ml of water/ethanol (1:1) together with 1.33 g (33.25 mmol) of sodium hydroxide pellets. 3.04 g (16.53 mmol) of butyl iodide were added and the mixture was stirred for 2 hours. The resulting S-alkylated product was treated with 3.96 g (18.14 mmol) of di-tert-butyl dicarbonate and the mixture was stirred for 1 hour. A further 3.61 g (16.53 mmol) of di-tert-butyl dicarbonate were added and the mixture was stirred overnight. The solution was evaporated to dryness under a vacuum and the residue was partitioned between diethyl ether and saturated aqueous sodium hydrogen carbonate solution. The aqueous phase was acidified by partitioning in 2M hydrochloric acid and ethyl acetate, the separated organic phase was dried over magnesium sulphate and the solvent was removed by evaporation to give 4.3 g of N-(tert-butoxycarbonyl)-S-butyl-L-cysteine as a brown oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.9 (t,3H), 1.3-1.6 (m,4H), 1.4 (s,9H), 2.55 (t,2H), 3.0 (br.d,2H), 4.5 (m,1H),

5.3 (br.d,1H).

ii) N,O-Dimethyl 2(R)-(tert-butoxyformamido)-3-(butylthio)-propionohydroxamate was obtained in a manner analogous to that described in Example 10 i) from 2.15 g (7.76 mmol) of N-(tert-butoxycarbonyl)-S-butyl-L-cysteine, 1.19 g (7.77 mmol) of 1-hydroxybenzotriazole monohydrate, 2.24 g (11.68 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 1.14 g (11.68 mmol) of N,O-dimethylhydroxylamine hydrochloride and 1.34 g (11.64 mmol) of N-ethylmorpholine in 30 ml of dichloromethane. This gave 2.0 g of product as a colourless oil after column chromatography using ethyl acetate/petrol (1:2) as the eluent. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.9 (t,3H), 1.3-1.6 (m,4H), 1.4 (s,9H), 2.55 (t,2H), 2.6 -2.7 (dd,1H), 2.8-2.9 (dd,1H), 3.2 (s,3H), 3.75 (s,3H), 4.8-4.9 (m,1H), 5.3 (br.d,1H).

iii) 0.3 g (0.94 mmol) of N,O-dimethyl 2(R)-(tert-butoxyformamido)-3-(butylthio)propionohydroxamate was dissolved in 10 ml of anhydrous tetrahydrofuran and the solution was cooled to 0°C. 0.55 ml (0.55 mmol) of a 1M solution of lithium aluminium hydride in tetrahydrofuran was added dropwise and the mixture was stirred for 15 minutes. The reaction was quenched by the dropwise addition of saturated aqueous potassium hydrogen sulphate and then 20 ml of diethyl ether were added. The mixture was stirred vigorously for 20 minutes. The organic phase was separated, washed with saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate and evaporated to give the aldehyde which, without further purification, was dissolved in 20 ml of saturated methanolic hydrogen chloride solution and stirred for 2 hours under a nitrogen atmosphere at room temperature. The solvent was removed by evaporation and the residue was re-evaporated twice with toluene to give the amino acid acetal as a brown oil.

200 mg (0.82 mmol) of the amino acid acetal were dissolved in 40 ml of dichloromethane and then 200 mg (0.22 mmol) of [N-[N-[N-[N-[N-[3-(tert-butoxycarbonyl) propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-

glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine, 100 mg (0.87 mmol) of N-ethylmorpholine, 40 mg (0.26 mmol) of 1-hydroxybenzotriazole and 50 mg (0.26 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added. The solution was stirred for 2 hours at room temperature. The organic phase was washed with 5% (w/v) aqueous citric acid solution and then with saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate and evaporated under a vacuum. The resulting oil was triturated with 10 ml of diethyl ether to give 160 mg of N2-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[2-(butylthio)-[1(R)-(dimethoxymethyl)ethyl]-L-leucinamide as a white solid; MS: m/e 1075.6 $[M+H-MeOH]^+$.

Example 12

56 mg (0.049 mmol) of N1-[2-(benzylthio)-1(R)-(dimethoxymethyl)ethyl]-N2-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucinamide were dissolved in 10 ml of trifluoroacetic acid/dichloromethane (1:1) containing 3 drops of water and the solution was stirred for 90 minutes. The solution was evaporated to dryness under a vacuum and the residue was re-evaporated twice with toluene. The solid was triturated with 10 ml of diethyl ether to give 40 mg of 3-(benzylthio)-2(R)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]propionaldehyde as a white solid. MS: m/e 927.6 $(M+H]^+$.

The starting material was prepared as follows:

i) S-Benzyl-N-(tert-butoxycarbonyl)-L-cysteine was obtained in a manner analogous to that described in Example 10 i) from 1 g (4.74 mmol) of S-benzyl-L-cysteine, 0.8 g (9.5 mmol) of sodium bicarbonate and 1.4 g (6.4 mmol) of di-tert-butyl dicarbonate. There were obtained 1.4 g of a colourless oil; ^1H NMR (250 MHz,

$CDCl_3$) δ: 1.4 (s,9H), 2.8-2.9 (m,2H), 3.7 (s,2H), 4.4-4.5 (m,1H), 5.3 (d,1H), 7.2-7.4 (m,5H)

ii) N,O-Dimethyl 3-(benzyl)-2(R)-(tert-butoxyformamido)-propionohydroxamate was obtained in a manner analogous to that described in Example 9 i) from 1.4 g (4.52 mmol) of S-benzyl-N-(tert-butoxycarbonyl)-L-cysteine, 0.70 g (4.6 mmol) of 1-hydroxybenzotriazole monohydrate, 1.30 g (6.77 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 0.66 g (6.77 mmol) of N,O-dimethylhydroxylamine hydrochloride and 0.78 g (6.77 mmol) of N-ethylmorpholine in 40 ml of dichloromethane. There were obtained 0.60 g of a colourless oil; ^1H NMR (250 MHz, $CDCl_3$) δ: 1.4 (s,9H), 2.55-2.65 (dd,1H), 2.75-2.85, (dd,1H), 3.2 (s,3H), 3.7 (s,3H), 3.72 (s,2H), 4.9 (m,1H), 5.3 (d,1H), 7.2 -7.35 (m,5H).

iii) 0.48 g (1.36 mmol) of N,O-dimethyl 3-(benzyl)-2(R)-(tert-butoxyformamido)propionohydroxamate was dissolved in 10 ml of anhydrous tetrahydrofuran and the solution was cooled to 0°C. 0.95 ml (0.95 mmol) of a 1M solution of lithium aluminium hydride in tetrahydrofuran was added dropwise and the mixture was stirred for 15 minutes. The reaction was quenched by the dropwise addition of saturated aqueous potassium hydrogen sulphate and then 20 ml of diethyl ether were added. The mixture was stirred vigorously for 20 minutes. The organic phase was separated, washed with saturated aqueous sodium bicarbonate solution, dried magnesium sulphate and evaporated to give the aldehyde which, without further purification, was dissolved in 10 ml of saturated methanolic hydrogen chloride solution and stirred for 2 hours at room temperature. The solvent was removed by evaporation and the residue was re-evaporated twice with toluene to give the amino acid acetal as a brown oil.

100 mg (0.36 mmol) of the amino acid acetal were dissolved in 40 ml of dichloromethane and then 200 mg (0.22 mmol) of N-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)-propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-

glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine, 100 mg (0.87 mmol) of N-ethylmorpholine, 40 mg (0.30 mmol) of 1-hydroxybenzotriazole and 50 mg (0.26 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride were added. The solution was stirred overnight at room temperature. The organic phase was washed with 5% (w/v) aqueous citric acid solution and then with saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate and evaporated under a vacuum. The resulting oil was triturated with 10 ml of diethyl ether to give 160 mg of N1-[2-(benzylthio)-1(R)-(dimethoxymethyl)ethyl]-N2-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucinamide as a white solid; MS: m/e 1109.8 $[M+H-MeOH]^+$.

Example 13

49 mg (0.046 mmol) of N2-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(S)-(dimethoxymethyl)-3-pentynyl]-L-leucinamide were dissolved in 4 ml of trifluoroacetic acid/dichloromethane (1:1) containing 3 drops of water and the solution was stirred for 1 hour under a nitrogen atmosphere. The solution was evaporated to dryness under a vacuum and the residue was re-evaporated twice with toluene. The solid was triturated with 10 ml of diethyl ether to give 30 mg of 2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4-hexynal as a white solid; MS: m/e 843.6 $[M+H]^+$.

The starting material was prepared as follows:

i) N-(tert-Butoxycarbonyl)-L-(2-butynyl)glycine was obtained in a manner analogous to that described in Example 10 i) from 1.0 g (7.80 mmol) of L-(2-butynyl)glycine (prepared according to Sasaki et al. Int. J. Peptide Protein Res 1986, 27, 360-365), 2.66 g (31.7 mmol) of sodium bicarbonate and 1.89 g

(8.66 mmol) of di-tert-butyl dicarbonate. There was obtained 1.94 g of a colourless oil; ^1H NMR (250 MHz, $CDCl_3$) δ: 1.45 (s,9H), 1.75 (t,3H), 2.6-2.9 (m,2H), 4.4-4.5 (m,1H), 5.3 (br.d,1H).

ii) N,O-Dimethyl 2(S)-(tert-butoxyformamido)-4-hexynohydroxamate was obtained in a manner analogous to that described in Example 9 i) from 1.74 g (7.67 mmol) of N-(tert-butoxycarbonyl)-L-(2-butynyl)glycine, 1.45 g (9.5 mmol) of 1-hydroxybenzotriazole, 2.06 g (10.73 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 1.05 g (10.77 mmol) of N,O-dimethylhydroxylamine hydrochloride and 5.3 ml (30.43 mmol) of ethyldiisopropylamine in 80 ml of tetrahydrofuran. There were obtained 2.0 g of a colourless oil; ^1H NMR (250 MHz, $CDCl_3$) δ: 1.4 (s,9H), 1.75 (t,3H), 2.55 (m,2H), 3.2 (s,3H), 3.5 (s,3H), 4.7-4.8 (m,1H), 5.35 (br.d,1H).

iii) 1.0 g (3.70 mmol) of N,O-dimethyl 2(S)-(tert-butoxyformamido)-4-hexynohydroxamate was dissolved in 10 ml of anhydrous tetrahydrofuran and the solution was cooled to 0°C. 2.59 ml (2.59 mmol) of a 1M solution of lithium aluminium hydride in tetrahydrofuran were added dropwise and the mixture was stirred for 30 minutes. The reaction was quenched by the dropwise addition of 20 ml of saturated aqueous potassium hydrogen sulphate and then 50 ml of diethyl ether were added. The mixture was stirred vigorously for 30 minutes. The organic phase was separated, washed with saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate and evaporated to give the aldehyde which, without further purification, was dissolved in 10 ml of saturated methanolic hydrogen chloride solution and stirred for 2 hours under a nitrogen atmosphere at room temperature. The solvent was removed by evaporation and the residue was re-evaporated twice with toluene to give the amino acid acetal as a brown oil.

47 mg (0.24 mmol) of the amino acid acetal were dissolved in 20 ml of dichloromethane and then 200 mg (0.22 mmol) of N-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenyl-

alanyl]-3-methyl-L-valyl]-L-leucine, 0.1 ml (0.78 mmol) of N-ethylmorpholine, 42 mg (0.27 mmol) of 1-hydroxybenzotriazole and 59 mg (0.31 mmol) of 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride were added. The solution was stirred overnight at room temperature. The organic phase was washed with 5% (w/v) aqueous citric acid solution and then with saturated aqueous sodium bicarbonate solution, dried over magnesium sulphate and evaporated under a vacuum. The resulting oil was triturated with 10 ml of diethyl ether to give 110 mg of N2-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(S)-(dimethoxymethyl)-3-pentynyl]-L-leucinamide as a white solid. MS: m/e 1025.8 $[M+H-MeOH]^+$.

Example 14

0.065 g (0.06 mmol) of N2-[N-[N-[N-[N-[3-(tert-butoxy-carbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(RS)-(dimethoxymethyl)-2-(3-thienyl)ethyl]-L-leucinamide was dissolved in 10 ml of dichloromethane/trifluoroacetic acid (1:1) containing 3 drops of water. The solution was stirred for 3 hours at room temperature. After removal of the solvent by evaporation the crude product was chromatographed on silica gel using dichloromethane:methanol:acetic acid:water (120:15:3:2) as the eluent to give 0.035 g of 2(RS)-[[N-[N-[N-[N-[N-(3-carboxy-propionyl)-L-α-aspartyl-L-α-glutamyl]-2-methyl-L-phenyl-alanyl]-3-methyl-L-valyl]-L-leucyl]amino]-3(3-thienyl)propion-aldehyde as a white solid; MS: m/e 887.7 $[M+H]^+$.

The starting material was prepared as follows:

i) 0.5 g (2.92 mmol) of 3-(3-thienyl)-DL-alanine was dissolved in 15 ml of water and 15 ml of dioxan. 2.5 g (29.76 mmol) of sodium hydrogen carbonate and 3.53 g (16.19 mmol) of di-tert-butyl dicarbonate were added and the solution was stirred for 2 hours and then evaporated to dryness

under a vacuum. The residue was partitioned between diethyl ether and saturated aqueous sodium hydrogen carbonate solution. The aqueous phase was acidified with 2M hydrochloric acid and extracted with ethyl acetate. The organic phase was dried over magnesium sulphate and the solvent was evaporated under a vacuum to give 0.685 g of N-(tert-butoxycarbonyl)-3-(3-thienyl)-DL-alanine as a colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.4 (s,9H), 2.9 (dd,1H), 3.15 (dd,1H), 4.3 (m,1H), 7.0 (d,1H), 7.1 (br s,H), 7.3 (m,1H).

ii) 0.69 g (2.55 mmol) of N-(tert-butoxycarbonyl)-3-(3-thienyl)-DL-alanine was dissolved in 40 ml of dichloromethane. 0.34 g (3.56 mmol) of N,O-dimethylhydroxylamine hydrochloride, 0.54 g (3.53 mmol) of 1-hydroxybenzotriazole monohydrate, 0.68 g (3.55 mmol) of 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride and 1.0 g (8.70 mmol) of 4-ethyl-morpholine were added and the resulting solution was stirred at room temperature overnight. The solution was then washed with 5% citric acid solution, saturated sodium hydrogen carbonate solution and saturated sodium chloride solution and dried over anhydrous magnesium sulphate. After evaporation of the solvent the crude product was chromatographed on silica gel using 30% ethyl acetate in petroleum ether as the eluent to give 0.75 g of N,O-dimethyl 2(RS)-(tert-butoxyformamido)-3-(3-thienyl)-propionohydroxamate as a white solid; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.4 (s,9H), 2.95 (dd,1H), 3.05 (dd,1H), 3.15 (s,3H), 3.65 (s,3H), 4.9 (m,1H), 5.15 (br d,1H), 6.9 (d,1H), 7.0 (d,1H), 7.2 (m,1H).

iii) 0.2 g (0.64 mmol) of N,O-dimethyl 2(RS)-(tert-butoxy-formamido)-3-(3-thienyl)propionohydroxamate was dissolved in 10 ml of anhydrous tetrahydrofuran and the solution was cooled to 0°C. 0.5 ml (0.5 mmol) of a 1M solution of lithium aluminium hydride in tetrahydrofuran was added dropwise and the solution was stirred for 15 minutes. The reaction was quenched by the dropwise addition of saturated potassium hydrogen sulphate solution and then 30 ml of diethyl ether were added. The resulting two phase system was stirred vigorously for 1 hour. The organic phase was separated, washed with saturated sodium

hydrogen carbonate solution and saturated sodium chloride solution, dried over magnesium sulphate and evaporated to give the aldehyde which, without purification, was dissolved in 10 ml of a saturated methanolic hydrogen chloride solution and stirred at room temperature for 2 hours. After removal of the solvent by evaporation the dimethyl acetal was used in the next step without purification.

The dimethyl acetal was dissolved in 40 ml of dichloromethane and then 0.15 g (0.16 mmol) of N-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine, 0.03 g (0.2 mmol) of 1-hydroxybenzotriazole, 0.038 g (0.2 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.08 g (0.65 mmol) of N-ethylmorpholine were added and the resulting solution was stirred at room temperature for 2 hours. The solution was washed with 5% citric acid solution, saturated sodium hydrogen carbonate solution and saturated sodium chloride solution and dried over anhydrous magnesium sulphate. After removal of the solvent by evaporation the crude product was chromatographed on silica gel using 5% methanol in dichloromethane as the eluent to give 0.07 g of N2-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(RS)-(dimethoxymethyl)-2-(3-thienyl)ethyl-L-leucinamide as a white solid; MS: m/e 1069 $[M+H-MeOH]^+$.

Example 15

0.08 g (0.07 mmol) of N2-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(S)-(dimethoxymethyl)-2-(2-thienyl)ethyl]-L-leucinamide was dissolved in 10 ml of dichloromethane/trifluoroacetic acid (1:1) containing 3 drops of water and the solution was stirred for 2 hours at room temperature. After removal of the solvent by evaporation the crude product was chromatographed on silica gel

using dichloromethane:methanol:acetic acid:water (120:15:3:2) as the eluent to give 0.021 g of 2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-3(2-thienyl)propionaldehyde as a white solid; MS: m/e 887.4 $[M+H]^+$.

The starting material was prepared as follows:

i) 0.63 g (2.33 mmol) of N-(tert-butoxycarbonyl)-3-(2-thienyl)-L-alanine was dissolved in 50 ml of dichloromethane and then 0.34 g (3.48 mmol) of N,O-dimethylhydroxylamine hydrochloride, 0.36 g (2.35 mmol) of 1-hydroxybenzotriazole monohydrate, 0.67 g (3.49 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.40 g (3.47 mmol) of N-ethylmorpholine were added. The resulting solution was stirred at room temperature overnight. The solution was washed with 5% citric acid, then with saturated sodium hydrogen carbonate solution and saturated sodium chloride solution, dried over anhydrous magnesium sulphate and evaporated to give 0.70 g of N,O-dimethyl 2(S)-(tert-butoxyformamido)-3-(2-thienyl)-propionohydroxamate as a white solid; ^1H NMR (250 MHz, $CDCl_3$) δ: 1.4 (s,9H), 3.1 (dd,1H), 3.15 (s,3H), 3.2 (dd,1H), 3.7 (s,3H), 4.9 (br d,1H), 5.8 (m,1H), 6.8 (d,1H), 6.9 (dd,1H), 7.15 (d,1H).

ii) 0.4 g (1.27 mmol) of N,O-dimethyl 2(S)-(tert-butoxyformamido)-3-(2-thienyl)propionohydroxamate was dissolved in 10 ml of anhydrous tetrahydrofuran and the solution was cooled to 0°C. 0.9 ml (0.9 mmol) of a 1M solution of lithium aluminium hydride in tetrahydrofuran was added and the resulting solution stirred for 15 minutes. The reaction was quenched by the dropwise addition of 15 ml of saturated potassium hydrogen sulphate solution and then 30 ml of diethyl ether were added. The resulting two phase system was stirred vigorously for 40 minutes. The organic phase was separated, washed with saturated sodium hydrogen carbonate solution and saturated sodium chloride solution and dried over anhydrous magnesium sulphate. After removal of the solvent by evaporation the aldehyde, without further purification, was dissolved in 10 ml of

a saturated methanolic hydrogen chloride solution and stirred at room temperature for 2 hours. After removal of the solvent by evaporation the dimethyl acetal was used in the next step without purification.

The dimethyl acetal was dissolved in 40 ml of dichloromethane and then 0.20 g (0.22 mmol) of N-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine, 0.04 mg (0.26 mmol) of 1-hydroxybenzotriazole, 0.05 g (0.26 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.10 g (0.87 mmol) of N-ethylmorpholine were added. The resulting solution was stirred at room temperature for 2 hours, then washed in sequence with 5% citric acid solution, saturated sodium hydrogen carbonate solution and saturated sodium chloride solution and dried over anhydrous magnesium sulphate. After removal of the solvent by evaporation the crude product was triturated with diethyl ether to give 0.16 g of N2-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)-propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(S)-(dimethoxymethyl)-2-(2-thienyl)ethyl-L-leucinamide as a white solid. MS: m/e 1069.6 $[M+H-MeOH]^+$.

Example 16

In an analogous manner to that described in Example 4, by replacing N-[(9-fluorenyl)methoxycarbonyl]-3-(2-naphthyl)-D-alanine with N-[(9-fluorenyl)methoxycarbonyl]-L-cyclohexylglycine there was obtained 2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-2-cyclohexylglycyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde as a white solid; MS: m/e 883.5 [M+H].

Example 17

In an analogous manner to that described in Example 4, by replacing N-[(9-fluorenyl)methoxycarbonyl]-3-(2-naphthyl)-D-

alanine with N-[(9-fluorenyl)methoxycarbonyl]-L-valine there was obtained 2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-valyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde as a white solid; MS: m/e 843.5 [M+H].

Example 18

In an analogous manner to that described in Example 4, by replacing N-[(9-fluorenyl)methoxycarbonyl]-3-(2-naphthyl)-D-alanine with N-[(9-fluorenyl)methoxycarbonyl]-D-alanine there was obtained 2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-D-alanyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde as a white solid; MS: m/e 815.4 [M+H].

Example 19

In an analogous manner to that described in Example 4, by replacing N-[(9-fluorenyl)methoxycarbonyl]-3-(2-naphthyl)-D-alanine with N-[(9-fluorenyl)methoxycarbonyl]-D-valine there was obtained 2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-D-valyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde as a white solid; MS: m/e 843.4 [M+H].

Example 20

0.2 g (0.2 mmol) of N2-[N-[N-[N-[N-(carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(R)-(3a(S),4(S),5,6(S),7,7a(R)-hexahydro-3a,5,5-trimethyl-4,6-methano-1,3,2-benzodioxaborol-2-yl)pentyl]-L-leucinamide was dissolved in 12 ml of acetone and 12 ml of 0.1M ammonium acetate in water were added. 0.21 g (1 mmol) of sodium periodate was added and the resulting mixture was stirred at room temperature for 22 hours. 7 ml of water were then added together with a small amount of sodium periodate. The resulting solution was stirred for a further 5 hours. The

acetone was removed under a vacuum and the aqueous residue was acidified with 2N hydrochloric acid and then extracted with ethyl acetate. Saturated aqueous sodium chloride was added to the aqueous layer which was then extracted with ethyl acetate. The organic extracts were combined, dried over sodium sulphate and evaporated. The residue was trituated with diethyl ether, filtered off and dried to give 167 mg of1(R)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]pentylboronic acid as a white solid; MS: m/e 845.4 $[M+H-H_2O]^+$.

The starting material was prepared as follows:

i) In an analogous manner to that described in Example 21 i) and ii), by replacing 3-butenylmagnesium bromide with butylmagnesium bromide there was obtained α-(R)-butyl-3a(S),4(S),5,6(S),7,7a(R)-hexahydro-3a,5,5-trimethyl-4,6-methano-1,3,2-benzodioxaborole-2-methylamine trifluoroacetate (1:1) which was used in the next step without further purification.

ii) 0.25 g (0.27 mmol) of N-[N-[N-[N-[N-(tert-butoxycarbonyl)-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine was dissolved in 2 ml of dimethylformamide and 4 ml of dichloromethane. 0.15 ml (1.4 mmol) of N-methylmorpholine was added and the solution was cooled to -10°C under a nitrogen atmosphere. 45 mg (0.32 mmol) of isobutyl chloroformate were added and the solution was stirred for 10 minutes at -10°C. 0.2 g (0.54 mmol) of α-(R)-butyl-3a(S),4(S),5,6(S),7,7a(R)-hexahydro-3a,5,5-trimethyl-4,6-methano-1,3,2-benzodioxaborole-2-methylamine trifluoroacetate (1.1) was added and the mixture was stirred at room temperature for 16 hours. The solution was diluted with dichloromethane, washed with 2M hydrochloric acid and water and dried over anhydrous sodium sulphate. After evaporation the residue was triturated with diethyl ether and dried. There was obtained 0.227 g of N2-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-

L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(R)-(3a(S), 4(S),5,6(S), 7,7a(R)-hexahydro-3a,5,5-trimethyl-4,6-methano-1,3,2-benzodioxaborol-2-yl)pentyl]-L-leucinamide as a white solid; MS: m/e 1165.9 [M+H]+.

iii) 300 mg (0.26 mmol) of N2-[N-[N-[N-[N-(tert-butoxycarbonyl)-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(R)-(3a(S),4(S),5,6(S),7,7a(R)-hexahydro-3a,5,5-trimethyl-4,6-methano-1,3,2-benzodioxaborol-2-yl)-4-pentenyl]-L-leucinamide were dissolved in 3.5 ml of trifluoroacetic acid and 3.5 ml of dichloromethane. The solution was stirred at room temperature for 45 minutes, then diluted with toluene and evaporated. The residue was triturated with diethyl ether and the resulting solid was filtered off and dried and then purified by chromatography on silica gel using dichlomethane/methanol/acetic acid/water (170:15:3:2) for the elution. There were obtained 135 mg of N2-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(R)-(3a(S), 4(S),5,6(S),7,7a(R)-hexahydro-3a,5,5-trimethyl-4,6-methano-1,3,2-benzodioxaborol-2-yl)-4-pentenyl]-L-leucinamide as a white solid: MS: m/e 995.3 [M+H]+.

Example 21

N2-[N-[N-[N-[N-(3-Carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(R)-(3a(S),4(S),5,6(S),7,7a(R)-hexahydro-3a,5,5-trimethyl-4,6-methano-1,3,2-benzodioxaborol-2-yl)-4-pentenyl]-L-leucinamide can be converted into N2-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4-pentenylboronic acid in an analogous manner to that described in the first paragraph of Example 20.

The starting material was prepared as follows:

i) 0.5 g (1.9 mmol) of 2-(dichloromethyl)-3a(S),4(S),5,6(S), 7,7a(R)-hexahydro-3a,5,5-trimethyl-4,6-methano-1,3,2-benzo-

dioxaborole was dissolved in 5 ml of tetrahydrofuran and the solution was cooled to -78°C under a nitrogen atmosphere. 4.5 ml (2.3 mmol) of 0.5M 3-butenylmagnesium bromide in tetrahydrofuran were added dropwise and the resulting solution was stirred for 2 minutes. 3 ml (1.52 mmol) of 0.5M zinc (II) chloride solution were then added and the mixture was stirred for 16 hours while slowly warming to room temperature. The mixture was diluted with ethyl acetate and then washed with 2M hydrochloric acid and brine. The organic phase was dried over sodium sulphate and then evaporated under a vacuum. The residue was purified by chromatography on silica gel using diethyl ether/hexane (1:9) for the elution to give 177 mg of 2-[1(S)-chloro-4-pentenyl]-3a(S)-4(S),5,6(S),7,7a(R)-hexahydro-3a,5,5-trimethyl-4,6-methano-1,3,2-benzodioxaborole. NMR: ($CDCl_3$) 0.83 (s, 3H), 1.15 (d, 1H, 1.30 (s, 3H), 1.42 (s, 3H), 1.42 (s, 3H), 1.85-1.95 (m, 4H), 2.08 (t, 1H), 2.15-2.35 (m, 4H), 3.49 (dd, 1H), 4.35 (dd, 1H), 5.0 (dd, 1H), 5.07 (dd, 1H), 5.78 (m, 1H).

ii) 0.158 g (0.56 mmol) of 2-[1(S)-chloro-4-pentenyl]-(3a(S),5,6(S),7,7a(R)-hexahydro-3a,5,5-trimethyl-4,6-methano-1,3,2-benzodioxaborole was dissolved in 2 ml of tetrahydrofuran and then cooled to -78°C under a nitrogen atmosphere. 0.56 ml (0.56 mmol) of 1M lithium bis(trimethylsilyl)amide in tetrahydrofuran was added dropwise. The solution was then stirred overnight while slowly warming to room temperature. The solvent was removed by evaporation and the residue was taken up in diethyl ether. Insoluble material was removed by filtration. The solvent was removed by evaporation, the residue was dissolved in 2 ml of diethyl ether and the solution was cooled to 0°C. 0.12 ml (1.7 mmol) of trifluoroacetic acid was added and the solution was stirred at 0°C for 30 minutes. The solution was evaporated and the residue was co-evaporated with toluene to give 0.0226 g of a-(R)-(3-butenyl)-3a(S),4(S),5,6(S),7, 7a(R)-hexahydro-3a,5,5-trimethyl-4,6-methano-1,3,2-benzodioxaborole-2-methylamine trifluoroacetate (1:1) as an oil which was used in the next step without further purification.

iii) 0.35 g (0.38 mmol) of N-[N-[N-[N-(tert-butoxycarbonyl)-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine was dissolved in 2 ml of dimethylformamide and 6 ml of dichloromethane. 0.21 ml (1.9 mmol) of N-methylmorpholine was added and the solution was cooled to -15°C under a nitrogen atmosphere. 66 mg (0.46 mmol) of isobutyl chloroformate were added and the solution was stirred for 10 minutes at -15°C. 0.2 g (0.53 mmol) of α-(R)-(3-butenyl)-3a(S),4(S),5,6(S),7,7a(R)-hexahydro-3a,5,5-trimethyl-4,6-methano-1,3,2-benzoxaborole-2-methylamine trifluoroacetate (1.1) was added and the mixture was stirred at room temperature for 5 hours. The solution was diluted with dichloromethane, washed with 2M hydrochloric acid and water and dried over anhydrous sodium sulphate. After evaporation the residue was triturated with diethyl ether and dried. There was obtained 0.309 g of N2-[N-[N-[N-[N-(tert-butoxycarbonyl)-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(R)-(3a(S),4(S),5,6(S),7,7a(S)-hexahydro-3a,5,5-trimethyl-4,6-methano-1,3,2-benzodioxaborol-2-yl)-4-pentenyl-L-leucinamide as as solid which was used without further purification.

iv) 300 mg (0.26 mmol) of N2-[N-[N-[N-[N-(tert-butoxy-carbonyl)-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl-3-methyl-L-valyl]-N1-[1(R)-(3a(S),4(S),5,6(S),7,7a(R)-hexahydro-3a,5,5-trimethyl-4,6-methano-1,3,2-benzodioxaborol-2-yl)-4-pentenyl]-L-leucinamide were dissolved in 3.5 ml of trifluoroacetic acid and 3.5 ml of dichloromethane. The solution was stirred at room temperature for 45 minutes, then diluted with toluene and evaporated. The residue was triturated with diethyl ether and the resulting solid was filtered off and dried and then purified by chromatography on silica gel using dichlomethane/methanol/acetic acid/water (170:15:3:2) for the elution. There were obtained 135 mg of N2-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(R)-(3a(S),4(S),5,6(S),7,7a(R)-hexahydro-3a,5,5-trimethyl-4,6-methano-1,3,2-benzodioxaborol-2-yl)-4-pentenyl]-L-leucinamide as a

white solid: MS: m/e 995.3 $[M+H]^+$.

Example 22

N2-[N-[N-[N-[N-(3-Carboxypropionyl)-L-α-aspartyl]-L-α-gluatamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(R)-(3a(S),4(S),5,6(S),7,7a(R)-hexahydro-3a,5,5-trimethyl-4,6-methano-1,3,2-benzodioxaborol-2-yl)propyl]-L-leucinamide can be converted into 1(R)-[[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]propylboronic acid in a manner analogous to that described in the first paragraph of Example 20.

The starting material was prepared as follows:

i) In an analogous manner to that described in Example 21 i) and ii), by replacing 3-butenylmagnesium bromide with ethylmagnesium bromide there was obtained α(R)-ethyl-3a(R)-ethyl-3a(S),4,(S),5,6(S),7,7a(R)-hexahydro-3a,5,5-trimethyl-4,6-methano-1,3,2-benzodioxaborole-2-methylamine trifluoroacetate (1:1) which was used in the next step without further purification.

ii) 0.35 g (0.38 mmol) of N-[N-[N-[N-[N-(tert-butoxycarbonyl)-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl-3-methyl-L-valyl]-L-valyl]-L-leucine was dissolved in 3 ml of dimethylformamide and 7 ml of dichloromethane. 0.2 ml (1.9 mmol) of N-methylmorpholine was added and the solution was cooled to -10°C under a nitrogen atmosphere. 68 mg (0.53 mmol) of isobutyl chloroformate were added and the solution was stirred for 10 minutes at -10°C. 0.18 g (0.53 mmol) of α(R)-ethyl-3a(S)4(S),5,6,(S),7,7a(R)-hexahydro-3a,5,5-trimethyl-4,6-methano-1,3,2-benzodioxaborole-2-methylamine trifluoroacetate (1:1) was added and the mixture was stirred at room temperature for 16 hours. After evaporation the residue was partitioned between ethyl acetate and 2M hydrochloric acid. The organic layer was washed with water and saturated sodium chloride solution and then dried over

anhydrous sodium sulphate. The solution was evaporated and the residue was triturated with diethyl ether, filtered off and dried to give 0.22 g of N2-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)-propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(R)-(3a(S),4(S),5,6(S),7,7a(R)-hexahydro-3a,5,5-trimethyl-4,6-methano-1,3,2-benzodioxaborol-2-yl)propyl]-L-leucinamide as a solid which was used without further purification.

iii) 0.22 g (0.19 mmol) of N2-[N-[N-[N-[N-[3-(tert-butoxy-carbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(R)-3a(S),4(S),5,6,(S),7,7a(R)-hexahydro-3a,5,5-trimethyl-4,6-methano-1,3,2-benzodioxaborol-2-yl)propyl]-L-leucinamide was dissolved in 5 ml of trifluoroacetic acid and 5 ml of dichloro-methane, the solution was stirred at room temperature for 1 hour and then diluted with toluene and evaporated. The residue was triturated with diethyl ether and the resulting solid was filtered off and dried to give 170 mg of N2-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-gluatamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(R)-(3a(S),4(S),5,6(S),7,7a(R)-hexahydro-3a, 5,5-trimethyl-4,6-methano-1,3,2-benzodioxaborol-2-yl)propyl]-L-leucinamide as a white solid; MS: m/e 969.4 $[M+H]^+$.

Example 23

4 g of 0.25 mmol/g 5-[2-[1(RS)-[[N-[(9-fluorenyl)methoxy-carbonyl]-L-leucyl]amino]propyl]-4(RS),5,5-trimethyl-1,3,2-dioxoborolan-4-yl]-3(RS)-methyl-N-[α(RS)-(4-methyl-phenyl)benzyl]valeramide-polystyrene conjugate were swollen in dimethylformamide for 20 minutes and then suspended and agitated in dimethylformamide/piperidine (4.1). After 5 minutes the resin was drained and then suspended in and agitated with dimethylformamide/piperidine (4.1) for a further 5 minutes. The resin was then drained and washed five times with dimethyl-formamide.

The resin was then suspended in a solution of 2.1 g (6 mmol) of N-[(9-fluorenyl)methoxycarbonyl]-3-methyl-L-valine in dimethylformamide and then a mixture of 1.9 g of 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate and 1.3 ml of N-methylmorpholine dissolved in dimethylformamide was added. After agitating for 40 minutes the resin was drained and washed five times with dimethylformamide.

The resin was resuspended in and agitated with dimethylformamide/piperidine (4:1). After 5 minutes the resin was drained and resuspended in and agitated with dimethylformamide/piperidine (4:1) for a further 5 minutes. Then, the residue was drained and washed five times with dimethyl formamide.

The resin was then suspended in a solution of 2.4 g (6 mmol) of N-[(9-fluorenyl)methoxycarbonyl]-3-(2-methylphenyl)-L-alanine in dimethylformamide and a mixture of 1.9 g of 2(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate and 1.3 ml of N-methylmorpholine dissolved in dimethylformamide was added. After agitating for 40 minutes the resin was drained and washed five times with dimethyl formamide.

40 mg of this resin were resuspended in and agitated with 0.7 ml of dimethylformamide/piperidine (4:1). After 5 minutes the resin was drained and resuspended in and agitated with dimethylformamide/ piperidine (4:1) for a further 5 minutes. Then, the resin was drained and washed five times with dimethylformamide.

The resin was then suspended in 0.5 ml of a 0.2M solution of N-[(9-fluorenyl)methoxycarbonyl]-O-tert-butyl-L-α-glutamic acid in dimethyl sulphoxide and then 0.5 ml of a mixture of 0.2M 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate and 0.4M N-methylmorpholine in dimethylformamide was added. After agitating for 1 hour the resin was drained and washed five times with 1 ml of dimethylformamide

The resin was resuspended in and agitated with 0.7 ml of dimethylformamide/piperidine (4:1). After 5 minutes the resin was drained and resuspended in and agitated with dimethylformamide/piperidine (4:1) for a further 5 minutes. Then, the resin was drained and washed five times with 1 ml of dimethylformamide.

The resin was suspended in 0.5 ml of a solution of N-(9-fluorenylmethoxycarbonyl)-O-tert-butyl-L-tyrosine in dimethyl sulphoxide and 0.5 ml of a mixture of 0.2M 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate and 0.4M N-methylmorpholine in dimethylformamide was added. After agitating for 1 hour the resin was drained and washed five times with 1 ml of dimethylformamide.

The resin was resuspended in and agitated with 0.7 ml of dimethylformamide/piperidine (4:1). After 5 minutes the resin was drained and resuspended in and agitated with dimethylformamide/piperidine (4:1) for a further 5 minutes. Then, the resin was drained and washed five times with 1 ml of dimethylformamide.

The residue was suspended in 0.5 ml of a 0.2M solution of tert-butyl hydrogen succinate in dimethylformamide and then 0.5 ml of 0.2M 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate and 0.4M N-methylmorpholine dissolved in dimethylformamide was added. After agitating for 1 hour the resin was drained and washed five times with 1 ml of dimethylformamide and then twice with 1 ml of dichloromethane.

0.2 ml of dichloromethane was added to the resin which was then treated with 0.7 ml of trifluoroacetic acid/water (19:1) and agitated for 90 minutes. The resin was then filtered off and washed with 0.7 ml of trifluoroacetic acid/water (19:1). The combined trifluoroacetic acid and water solutions were then evaporated in a vacuum centrifuge and the residue was suspended in acetonitrile/water (1:1) and freeze dried. There were obtained

16.8 mg of 1(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-tyrosyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]propylboronic acid as a white solid; MS m/e 807.4 $[M+H-H_2O]^+$.

The starting material was prepared as follows:

i) 25 ml of isobutylene were condensed at -78°C and added to a mixture of 19.4 g (114 mmol) of 3(RS),7-dimethyl-6-octenoic acid and 1 ml of concentrated sulphuric acid in 25 ml of dichloromethane. The mixture was stirred for 24 hours under a dry ice condenser. A further 20 ml of isobutylene were added and the mixture was stirred for 24 hours under a dry ice condenser. The mixture was diluted with dichloromethane, washed with saturated sodium bicarbonate solution, dried over anhydrous magnesium sulphate and evaporated under a vacuum. The resulting oil was purified by chromatography on silica gel using ethyl acetate/hexane (1:9) for the elution. There were obtained 20.8 g of tert-butyl 3(RS),7-dimethyl-6-octenoate as a colourless oil. ^1H NMR (250 MHz, $CDCl_3$) d: 0.9 (d, 3H), 1.1-1.3 (m, 3H), 1.4 (s, 9H), 1.6 (s, 3H), 1.65, (s, 3H), 1.8-2.2 (br m, 4H), 5.05, (m, 1H).

ii) 1.5 g (6.64 mmol) of tert-butyl 3(RS),7-dimethyl-6-octenoate were dissolved in a mixture of 10 ml of acetone, 2 ml of water and 2 ml of glacial acetic acid. 2 g (12.6 mmol) of potassium permanganate were added and the resulting mixture was stirred at 30°C for 2 hours. 22 ml of 2M sulphuric acid and 0.8 g (11.3 mmol) of sodium nitrite were added and the organic phase was separated. The aqueous phase was extracted with dichloromethane and the combined organic phases were washed with water, dried over magnesium sulphate and evaporated under a vacuum to give 1.55 g of tert-butyl 7-hydroxy-3(RS),7-dimethyl6-oxo-octenoate as a clear oil; MS: m/e 259 $[M+H]^+$.

iii) 0.25 g (0.97 mmol) of tert-butyl 7-hydroxy-3(RS),7-dimethyl-6-oxo-octenoate was dissolved in 3 ml of diethyl ether at 0°C under a nitrogen atmosphere. 0.36 ml (1.1 mmol) of 3M

methylmagnesium bromide in diethyl ether was added dropwise and the resulting solution was stirred at 0°C for 2 hours, refluxed for 6 hours and then stirred at room temperature for 16 hours. The solution was diluted with ethyl acetate and then extracted with 2M hydrochloric acid and saturated sodium chloride solution. The organic phase was dried over anhydrous sodium sulphate and evaporated under a vacuum. The resulting oil was purified by chromatography on silica gel using ethyl acetate/ hexane (1:2) for the elution. There were obtained 118 mg of tert-butyl 6(RS),7-dihydroxy-3(RS),6,7-trimethyl-6-octenoate as a clear oil; MS: m/e 275 $[M+H]^+$.

iv) 0.64 g (2.3 mmol) of tert-butyl 6(RS),7-dihydroxy-3-(RS), 6,7-trimethyl-6-octenoate was stirred in 3 ml of tetrahydrofuran with 0.5 g (2.5 mmol) of dichloromethyl diisopropoxyborane at room temperature for 16 hours. The resulting mixture was evaporated and the residue was co-evaporated with toluene to give 0.86 g of tert-butyl 5-[2-(dichloromethyl)-4(RS),5,5-trimethyl-1,3,2-dioxaborolan-4-yl]-3(RS)-methylvalerate as an oil which was used in the next step without further purification.

v) 0.86 g (2.3 mmol) of tert-butyl 5-[2-(dichloromethyl)-4(RS), 5,5-trimethyl-1,3,2-dioxaborolan-4-yl]-3(RS)-methylvalerate was dissolved in 5 ml of tetrahydrofuran and the solution was cooled to -78°C under a nitrogen atmosphere. 2.6 ml (2.6 mmol) of 1M ethylmagnesium bromide in tetrahydrofuran were added dropwise, the resulting solution was stirred for 16 hours while slowly warming to room temperature and then diluted with ethyl acetate and extracted with 2M hydrochloric acid and brine. The organic phase was dried over sodium sulphate and then evporated under a vacuum to give 0.83 g of tert-butyl 5-[2-(1(RS)-chloropropyl)-4(RS),5,5-trimethyl-1,3,2-dioxaborolan-4-yl]-3(RS)-methylvalerate as an oil which was used in the next step without purification.

vi) 0.82 g (2.27 mmol) of tert-butyl 5-[2-(1(RS)-chloropropyl)-4(RS),5,5-trimethyl-1,3,2-dioxaborolan-4-yl]-3(RS)-methylvalerate was dissolved in 10 ml of tetrahydrofuran and

then cooled to -78°C under a nitrogen atmosphere. 2.3 ml (2.3 mmol) of 1M lithium bis(trimethylsilyl)amide in tetrahydrofuran were added dropwise. The solution was then stirred overnight while slowly warming to room temperature. The solvent was removed by evaporation and the residue was taken up in diethyl ether. Insoluble material was removed by filtration and the filtrate was cooled to 0°C. 0.52 ml (6.8 mmol) of trifluoroacetic acid was added and the solution was stirred at 0°C for 30 minutes. The solution was evaporated and the residue was co-evaporated with toluene to give 1 g of tert-butyl 5-[2-(1(RS)-aminopropyl)-4(RS), 5,5-trimethyl-1,3,2-dioxaborolan-4-yl]-3(RS)-methylvalerate as an oil which was used in the next step without purification.

vii) 0.5 g (1.42 mmol) of N-[(9-fluorenyl)methoxycarbonyl]-L-leucine was dissolved in 7 ml of dichloromethane. 0.6 ml (5.7 mmol) of N-methylmorpholine was added and the solution was cooled to -10°C under a nitrogen atmosphere. 0.22 ml (1.7 mmol) of isobutyl chloroformate was added and the solution was stirred for 7 minutes at -10°C. 1 g (2.13 mmol) of tert-butyl 5-[2-(1(RS)-aminopropyl)-4(RS),5,5-trimethyl-1,3,2-dioxaborolan-4-yl]-3(RS)-methylvalerate was added and the mixture was stirred at room temperature for 16 hours, then diluted with dichloromethane and extracted with 2M hydrochloric acid. The organic phase was extracted with 2M hydrochloric acid and saturated sodium hydrogen carbonate solution and then dried over anhydrous magnesium sulphate. After evaporation the residue was purified by chromatography on silica gel using ethyl acetate/hexane (1:2) for the elution. There was obtained 0.56 g of tert-butyl 5-[2-[1(RS)-[[N-[(9-fluorenyl)methoxycarbonyl]-L-leucyl]amino]propyl]-4(RS),5,5-trimethyl-1,3,2-dioxaborolan-4-yl]-3(RS)-methylvalerate as an oil; MS: m/e 677 [M+H]+.

viii) 50 mg (0.074 mmol) of tert-butyl 5-[2-[1(RS)-[[N-[(9-fluorenyl)methoxycarbonyl]-L-leucyl]amino]propyl]-4(RS),5,5-trimethyl-1,3,2-dioxaborolan-4-yl]-3(RS)-methylvalerate were dissolved in 1 ml of trifluoroacetic acid and 1 ml of dichloromethane. The solution was stirred at room temperature for

15 minutes and then evaporated under a vacuum. The residue was co-evaporated with toluene to give 46 mg of 5-[2-[1(RS)-[[N-[(9-fluorenyl)methoxycarbonyl]-L-leucyl]amino]propyl]-4(RS),5,5-trimethyl-1,3,2-dioxaborolan-4-yl]-3(RS)-methylvaleric acid as an oil; MS: m/e 621 [M+H]+.

ix) 5 g (5.25 mmol) of 4-methylbenzhydrylamine resin were swollen in dimethylformamide and excess solvent was drained from the resin. The resin was then resuspended in dimethylformamide containing 3.4 g (5.48 mmol) of 5-[2-[1(RS)-[[N-[(9-fluorenyl)methoxycarbonyl]-L-leucyl]amino]propyl]-4(RS),5,5-trimethyl-1,3,2-dioxaborolan-4-yl]-3(RS)-methylvaleric acid and 3 g (8.2 mmol) of 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate. Thereto there were added 3.0 ml (16.5 mmol) of diisopropylamine. The resulting mixture was agitated for 100 minutes and the resin was then drained and washed three times with dimethylformamide. The resin was then resuspended in dimethylformamide containing 5 ml (54.8 mmol) of acetic anhydride and 11.5 ml (110 mmol) of N-methylmorpholine. The mixture was agitated for 30 minutes and the resin was then drained. The resin was then resuspended in dimethylformamide containing 5 ml (54.8 mmol) of acetic anhydride and 11.5 ml (110 mmol) of N-methylmorpholine. The mixture was agitated for 30 minutes and the resin was then drained and washed three times with dimethylformamide, twice with ethyl acetate, twice with dichloromethane and twice with diethyl ether and then dried under a vacuum. After drying there was obtained 6 g of 5-[2-[1(RS)-[[N-[(9-fluorenyl)methoxycarbonyl]-L-leucyl]-amino]propyl] -4-(RS),5,5-trimethyl-1,3,2-dioxoborolan-4-yl]-3(RS)-methyl-N-[α(RS)-(4-methylphenyl)benzyl]valeramide-polystyrene conjugate as a pale brown solid (0.25 mmol/g loading estimated by quantitation of dibenzofulvene at 301 nM).

Example 24

In an analogous manner to that described in Example 5, from N2-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenyl-

alanyl]-3-methyl-L-valyl]-3-cyclopentyl-N1-[1(RS)-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-butenyl]-L-alaninamide there was obtained 1(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-3-cyclopentyl-L-alanyl]amino]-3-butenylboronic acid as a white solid; MS: m/e 855 [M+H-H_2O].

The starting material was prepared as follows:

i) A mixture of 1.2 g (4.67 mmol) of N-(tert-butoxy-carbonyl)-3-cyclopentyl-L-alanine, 540 mg (5 mmol) of benzyl alcohol, 675 mg (5 mmol) of 1-hydroxybenzotriazole, 1.152 g (6 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.031 g (0.25 mmol) of 4-dimethylamino-pyridine was stirred in 20 ml of dichloromethane for 1 hour and then a further 610 mg (5 mmol) of 4-dimethylaminopyridine were added. After 4 hours the solution was extracted with 2M hydrochloric acid and saturated sodium bicarbonate solution, dried over anhydrous magnesium sulphate and evaporated. The oil obtained was chromatographed on silica gel using ethyl acetate/ petrol (1:6) for the elution to give 1.55 g of N-(tert-butoxy-carbonyl)-3-cyclopentyl-L-alanine benzyl ester as a colourless oil; MS: m/e 348 [M+H].

ii) 1.54 g (4.44 mmol) of N-(tert-butoxycarbonyl)-3-cyclo-pentyl-L-alanine benzyl ester and 2.53 g (13.32 mmol) of 4-toluenesulphonic acid hydrate were dissolved in 20 ml of aceto-nitrile and the solution was left to stand at room temperature for 18 hours. The white precipitate formed was filtered off and added to a mixture of 867 mg (3.75 mmol) of N-(tert-butoxy-carbonyl)-3-methyl-L-valine, 557 mg (3.64 mmol) of 1-hydroxy-benzotriazole, 793 mg (4.14 mmol) of 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride and 475 mg (4.13 mmol) of N-ethylmorpholine in 25 ml of dichloromethane and stirred at room temperature for 18 hours. The solution was extracted with 2M hydrochloric acid and saturated sodium bicarbonate solution and then dried over anhydrous magnesium sulphate. Evaporation and chromatography on silica gel using

ethyl acetate/petrol (1:3) for the elution gave 1.06 g of N-[N-(tert-butoxycarbonyl)-3-methyl-L-valyl]-3-cyclopentyl-L-alanine benzyl ester as an off-white foam; MS: m/e 461 [M+H].

iii) 993 mg (2.16 mmol) of N-[N-(tert-butoxycarbonyl)-3-methyl-L-valyl]-3-cyclopentyl-L-alanine benzyl ester and 1.23 g (6.47 mmol) of 4-toluenesulphonic acid hydrate were dissolved in 20 ml of acetonitrile and the solution was stirred at room temperature for 2 hours. The solvent was removed by evaporation and the residue was triturated with diethyl ether and filtered off. The solid obtained was added to a mixture of 602 mg (2.16 mmol) of N-(tert-butoxycarbonyl)-2-methyl-L-phenylalanine, 338 mg (2.21 mmol) of 1-hydroxybenzotriazole, 576 mg (3 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 345 mg (3 mmol) of N-ethylmorpholine in 20 ml of dichloromethane and stirred at room temperature for 18 hours. The solution was extracted with 2M hydrochloric acid and saturated sodium bicarbonate solution, then dried over anhydrous magnesium sulphate and evaporated. Chromatography of the residue on silica gel using ethyl acetate/petrol (3:7) for the elution gave 990 mg of N-[N-[N-(tert-butoxycarbonyl)-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-3-cyclopentyl-L-alanine benzyl ester as a white solid; MS: m/e 622 [M+H].

iv) 980 mg (1.578 mmol) of N-[N-[N-(tert-butoxycarbonyl)-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-3-cyclopentyl-L-alanine benzyl ester and 900 mg (4.73 mmol) of 4-toluenesulphonic acid hydrate were dissolved in 16 ml of acetonitrile and the solution was stirred at room temperature for 2 hours. The solvent was removed by evaporation and the residue was triturated with diethyl ether and filtered off. The solid obtained was added to a mixture of 671 mg (1.578 mmol) of N-(9-fluorenylmethoxycarbonyl)-O-tert-butyl-L-α-glutamic acid, 247 mg (1.614 mmol) of 1-hydroxybenzotriazole, 419 mg (2.19 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 252 mg (2.19 mmol) of N-ethylmorpholine in 16 ml of dichloromethane and stirred at room temperature for 18 hours. The solution was extracted with 2M hydrochloric acid and

saturated sodium bicarbonate solution and then dried over anhydrous magnesium sulphate. Evaporation and chromatography on silica gel using methanol/dichloromethane (1:49) for the elution gave 530 mg of N-[N-[N-[O-tert-butyl-N-(9-fluorenyl-methoxycarbonyl)-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-3-cyclopentyl-L-alanine benzyl ester as a white solid; MS: m/e 929 [M+H].

v) A solution of 520 mg (0.56 mmol) of N-[N-[N-[O-tert-butyl-N-[(9-fluorenyl)methoxycarbonyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-3-cyclopentyl-L-alanine benzyl ester in 3 ml of piperidine and 12 ml of dichloromethane was stirred at room temperature for 30 minutes. The solvent was removed by evaporation and the residue was chromatographed on silica gel using firstly ethyl acetate/petrol (1:1) and then methanol/dichloromethane (1:9) for the elution. The resulting amine was added to a solution of 207 mg (0.504 mmol) of N-(9-fluorenylmethoxycarbonyl)-O-tert-butyl-L-α-aspartic acid, 78 mg (0.51 mmol) of 1-hydroxybenzotriazole and 134 mg (0.7 mmol) of 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride in 10 ml of dichloromethane and stirred at room temperature for 18 hours. The solution was then extracted with 2M hydrochloric acid and saturated sodium bicarbonate solution and dried over anhydrous magnesium sulphate. Evaporation, trituration with diethyl ether and filtration gave 440 mg of N-[N-[N-[N-O-tert-butyl-N-[(9-fluorenyl)methoxycarbonyl]-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-3-cyclopentyl-L-alanine benzyl ester as a white solid; MS: m/e 1101 [M+H].

vi) A solution of 430 mg (0.39 mmol) of N-[N-[N-[N-O-tert-butyl-N-[(9-fluorenyl)methoxycarbonyl]-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-3-cyclopentyl-L-alanine benzyl ester in 4 ml of piperidine and 16 ml of dichloromethane was stirred at room temperature for 30 minutes and then evaporated. The residue was chromatographed on silica gel using firstly ethyl acetate/petrol (1:1) and

then methanol/dichloromethane (1:9) for the elution. The amine obtained was added to a solution of 174 mg (1 mmol) of tert-butyl hydrogen succinate, 135 mg (1 mmol) of 1-hydroxy-benzotriazole and 192 mg (1 mmol) of 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride in 15 ml of dichloro-methane and the mixture was stirred at room temperature for 18 hours, extracted with 2M hydrochloric acid and saturated sodium bicarbonate solution and then dried over anhydrous magnesium sulphate. Evaporation and chromatography on silica gel using methanol/dichloromethane (1:24) for the elution followed by trituration with diethyl ether gave 240 mg of N-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-3-cyclopentyl-L-alanine benzyl ester as a white solid; MS: m/e 1035 [M+H].

vii) A solution of 230 mg (0.223 mmol) of N-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-3-cyclopentyl-L-alanine benzyl ester in 10 ml of dimethylformamide was hydrogenated over 25 mg of 10% palladium/carbon for 3 hours. The catalyst was removed by filtration, the filtrate was evaporated and the residue was triturated with diethyl ether to give 206 mg of N-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-3-cyclopentyl-L-alanine as a white solid; MS: m/e 944 [M+H].

viii) 163 mg (0.173 mmol) of N-[N-[N-[N-[N-[3-(tert-butoxy-carbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-3-cyclopentyl-L-alanine were dissolved in 2 ml of dimethyl-formamide and 4 ml of dichloromethane. 80 mg (0.69 mmol) of N-ethylmorpholine were added and the solution was cooled to -10°C. 26 mg (0.19 mmol) of isobutyl chloroformate were added and the solution was stirred for 30 minutes at -10°C. 107 mg (0.345 mmol) of α-(RS)-allyl-4,4,5,5-tetramethyl-1,3,2-

dioxaborolane-2-methylamine trifluoroacetate in 1 ml of dichloromethane were added and the mixture was stirred at -10°C for 30 minutes and at room temperature for 3 hours. The solution was extracted with 2M hydrochloric acid and saturated sodium bicarbonate solution and then dried over anhydrous magnesium sulphate. Evaporation and chromatography on silica gel using methanol/dichloromethane (1:24) for the elution gave 54 mg of N2-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-3-cyclopentyl-N1-[1(RS)-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-butenyl]-L-alaninamide as a white solid; MS: m/e 1024 [M+H-$C_6H_{12}O$].

Example 25

In an analogous manner to that described in Example 5, from N2-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-cyclohexyl-L-alanyl]-N1-[1(RS)-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-butenyl-L-leucinamide, MS: m/e 1037 [M+H-$C_6H_{12}O$], there was obtained 1(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-cyclohexyl-L-alanyl]-L-leucyl]amino]-3-butenylboronic acid; MS: m/e 869 [M+H-H_2O].

The starting material was prepared in an analogous manner to that described in Example 5 via the following intermediates:

i) N-[N-(tert-Butoxycarbonyl)-3-cyclohexyl-L-alanyl]-L-leucine benzyl ester; MS: m/e 475 [M+H];

ii) N-[N-[N-(tert-butoxycarbonyl)-2-methyl-L-phenylalanyl]-3-cyclohexyl-L-alanyl]-L-leucine benzyl ester; MS: m/e 636 [M+H];

iii) N-[N-[N-[O-tert-butyl-N-[(9-fluorenyl)methoxycarbonyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-cyclohexyl-L-alanyl]-L-leucine benzyl ester; MS: m/e 944 [M+H];

iv) N-[N-[N-[N-[O-tert-butyl-N-[(9-fluorenyl)methoxycarbonyl]-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-cyclohexyl-L-alanyl]-L-leucine benzyl ester; MS: m/e 1114 [M+H];

v) N-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-cyclohexyl-L-alanyl]-L-leucine benzyl ester; MS: m/e 1049 [M+H]; and

vi) N-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-cyclohexyl-L-alanyl]-L-leucine; MS: m/e 958 [M+H].

Example 26

In an analogous manner to that described in Example 5, from N2-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-L-2-phenylglycyl]-N1-[1(RS)-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-butenyl-L-leucinamide, MS: m/e 1017 [M+H-$C_6H_{12}O$], there was obtained 1(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-L-2-phenylglycyl]-L-leucyl]amino]-3-butenylboronic acid; MS: m/e 849 [M+H-H_2O].

The starting material was prepared in an analogous manner to that described in Example 5 via the following intermediates:

i) N-[N-(tert-Butoxycarbonyl)-L-2-phenylglycyl]-L-leucine benzyl ester; MS: m/e 455 [M+H];

ii) N-[N-[N-(tert-butoxycarbonyl)-2-methyl-L-phenylalanyl]-L-2-phenylglycyl]-L-leucine benzyl ester; MS: m/e 616 [M+H];

iii) N-[N-[N-[O-tert-butyl-N-[(9-fluorenyl)methoxycarbonyl]-L-

α-glutamyl]-2-methyl-L-phenylalanyl]-L-2-phenylglycyl]-L-leucine benzyl ester; MS: m/e 923 [M+H];

iv) N-[N-[N-[N-[O-tert-butyl-N-[(9-fluorenyl)methoxycarbonyl]-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-L-2-phenylglycyl]-L-leucine benzyl ester; MS: m/e 1094 [M+H];

v) N-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-L-2-phenylglycyl]-L-leucine benzyl ester; MS: m/e 1028 [M+H]; and

vi) N-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-L-2-phenylglycyl]-L-leucine; MS: m/e 938 [M+H].

Example 27

In an analogous manner to that described in Example 5, from N2-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-L-2-cyclohexylglycyl]-N1-[1(RS)-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-butenyl-L-leucinamide, MS: m/e 1023 [M+H-$C_6H_{12}O$], there was obtained 1(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-L-2-cyclohexylglycyl]-L-leucyl]amino]-3-butenylboronic acid; MS: m/e 855 [M+H-H_2O].

The starting material was prepared in an analogous manner to that described in Example 5 via the following intermediates:

i) N-[N-(tert-Butoxycarbonyl)-L-2-cyclohexylglycyl]-L-leucine benzyl ester; MS: m/e 461 [M+H];

ii) N-[N-[N-(tert-butoxycarbonyl)-2-methyl-L-phenylalanyl]-L-2-cyclohexylglycyl]-L-leucine benzyl ester; MS: m/e 622 [M+H];

iii) N-[N-[N-[O-tert-butyl-N-[(9-fluorenyl)methoxycarbonyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-L-2-cyclohexylglycyl]-L-leucine benzyl ester; MS: m/e 929 [M+H];

iv) N-[N-[N-[N-[O-tert-butyl-N-[(9-fluorenyl)methoxycarbonyl]-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-L-2-cyclohexylglycyl]-L-leucine benzyl ester; MS: m/e 1100 [M+H];

v) N-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-L-2-cyclohexylglycyl]-L-leucine benzyl ester; MS: m/e 1034 [M+H]; and

vi) N-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-L-2-cyclohexylglycyl]-L-leucine; MS: m/e 944 [M+H].

Example 28

In an analogous manner to that described in Example 5, from N2-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(RS)-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-butenyl-L-prolinamide, MS: m/e 981 [M+H-$C_6H_{12}O$], there was obtained 1(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-prolyl]amino]-3-butenylboronic acid as a white solid; MS: m/e 813 [M+H-H_2O].

The starting material was prepared in an analogous manner to that described in Example 5 via the following intermediates:

i) N-[N-(tert-Butoxycarbonyl)-3-methyl-L-valyl]-L-proline benzyl ester;

ii) N-[N-[N-(tert-butoxycarbonyl)-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-proline benzyl ester;

iii) N-[N-[N-[O-tert-butyl-N-[(9-fluorenyl)methoxycarbonyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-proline benzyl ester;

iv) N-[N-[N-[N-[O-tert-butyl-N-[(9-fluorenyl)methoxycarbonyl]-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-proline benzyl ester;

v) N-[N-[N-[N-[O-tert-butyl-N-[3-(tert-butoxycarbonyl)-propionyl]-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl-L-proline benzyl ester; MS: m/e 992 [M+H]; and

vi) N-[N-[N-[N-[O-tert-butyl-N-[3-(tert-butoxycarbonyl)-propionyl]-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl-L-proline.

Example 29

In an analogous manner to that described in Example 5, from N2-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-L-phenylalanyl]-N1-[1(RS)-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-butenyl-L-leucinamide, MS: m/e 1031 [M+H-$C_6H_{12}O$], there was obtained 1(RS)-[[N-[N-[N-[N-[N-(3-carboxy-propionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-L-phenylalanyl]-L-leucyl]amino]-3-butenylboronic acid as a white solid; MS: m/e 863 [M+H-H_2O].

The starting material was prepared in an analogous manner to that described in Example 5 via the following intermediates:

i) N-[N-[N-[O-tert-Butyl-N-[(9-fluorenyl)methoxycarbonyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-L-phenylalanyl]-L-leucine benzyl ester;

ii) N-[N-[N-[N-[O-tert-butyl-N-[(9-fluorenyl)methoxy-carbonyl]-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-L-phenylalanyl]-L-leucine benzyl ester;

iii) N-[N-[N-[N-N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-L-phenylalanyl]-L-leucine benzyl ester; MS m/e 1042 [M+H]; and

iv) N-[N-[N-[N-N-[3-(tert-butoxycarbonyl)propionyl]-3-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-L-phenylalanyl]-L-leucine.

Example 30

0.04 g (0.03 mmol) of (E)-N2-[N-[N-[N-[N-(tert-butoxy-carbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(S)-(dimethoxymethyl)-3-pentyl]-L-leucinamide was dissolved in 4 ml of à 1:1 solution of dichloromethane and trifluoroacetic acid containing 3 drops of water. The resulting solution was stirred at room temperature for 1 hour. After removal of the solvent by evaporation and trituration of the residue with diethyl ether there was obtained 0.014 g of (E)-2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4-hexenal; MS: m/e 845.7 $[M+H]^+$.

The starting material was prepared as follows:

i) 25 g (347 mmol) of trans-2-buten-1-ol were dissolved in 750 ml of anhydrous diethyl ether. 7.25 ml (89.63 mmol) of anhydrous pyridine were added and the resulting solution was cooled to 0°C. 88.25 ml of phosphorus tribromide were added dropwise and the mixture was stirred for 2 hours at 0°C. The reaction was quenched by pouring the solution on to ice. The organic phase was washed with saturated sodium chloride

solution and dried over anhydrous magnesium sulphate. After removal of the solvent by evaporation there was obtained (E)-1-bromo-2-butane which was used in the next step without purification.

ii) 3.86 g (168 mmol) of sodium metal were dissolved in 106 ml of anhydrous ethanol. 36.35 g (168 mmol) of diethyl acetamidomalonate dissolved in 225 ml of anhydrous ethanol were added and the mixture was heated under reflux for 10 minutes. 22.66 g (168 mmol) of (E)-1-bromo-2-butene were added dropwise at room temperature and the mixture was stirred overnight and then evaporated to dryness under a vacuum. The residue was partitioned between ethyl acetate and 0.1M hydrochloric acid. The organic phase was washed with saturated sodium hydrogen carbonate solution and then with saturated sodium chloride solution and dried over anhydrous magnesium sulphate. The solvent was evaporated to give 40 g of diethyl (E)-2-acetamido-2-(2-butenyl)malonate as a colourless oil; ^1H NMR (250 MHz, $CDCl_3$) d: 1.25 (t, 6H), 1.6 (d, 3H), 2.0 (s, 3H), 2.9 (d, 2H), 4.2 (q, 4H), 5.15 (m, 1H) 5.5 (m, 1H), 6.7 s, 1H).

iii) 39.63 g (146 mmol) of diethyl (E)-2-acetamido-2-(2-butenyl)malonate were dissolved in 200 ml of ethanol and a solution of 19.24 g (481 mmol) of sodium hydroxide in 100 ml of water was added. The mixture was stirred for 2 hours at 60°C, evaporated to dryness under a vacuum and the residue was partitioned between diethyl ether and water. The aqueous phase was acidified with 2M hydrochloric acid and extracted with ethyl acetate. The organic phase was dried over magnesium sulphate and the solvent was removed by evaporation under a vacuum to give 26.1 g of (E)-2-acetamido-2-(2-butenyl)malonic acid as a white solid which was used in the next step without further purification. ^1H NMR (250 MHz, MeOD) δ: 1.65 (d, 3H), 2.0 (s, 3H), 2.9 (d, 2H), 5.25 (m, 1H), 5.5 (m, 1H).

iv) 26.1 g (121 mmol) of (E)-2-acetamido-2-(butenyl)malonic acid were dissolved in 200 ml of toluene. 34 ml (242 mmol) of triethylamine were added and the mixture was heated under

reflux for 1 hour. The solution was extracted with 1M hydrochloric acid and the aqueous layer was extracted with ethyl acetate. The combined organic phases were dried over magnesium sulphate and the solvent was removed under a vacuum to give 18.73 g of (E)-N-acetyl-DL-2-(2-butenyl)glycine as a white solid which was used in the next step without purification. ^1H NMR (250 Hz, MeOD) δ: 1.65 (d, 3H), 2.0 (s, 3H), 2.4 (m, 2H), 4.3 (m, 1H), 5.4 (m, 1H), 5.5 (m, 1H).

v) 9 g (52.63 mmol) of (E)-N-acetyl-DL-2-(2-butenyl)glycine were dissolved in 100 ml of water and the pH adjusted to 7.5 using ammonia solution. 0.09 g of acylase I extracted from porcine kidney, and 0.042 g (0.3 mmol) of cobalt (II) chloride were added and the mixture was stirred at 37°C overnight. A further 0.09 g of acylase I extracted from porcine kidney was added and the pH adjusted to 7.5 using ammonia solution. The mixture was stirred at 37°C overnight and the solution was then heated at 80°C for 30 minutes and was then acidified to pH 1 using 2 M hydrochloric acid. The solvent was removed by evaporation under vacuum and the crude product purified by trituration using ethyl acetate to yield 4.2 g of (E)-L-2-(2-butenyl)-glycine hydrochloride. ^1H NMR (250 MHz, D_2O) δ: 1.7 (d, 3H), 2.6 (m, 2H), 4.0 (m, 1H), 5.35 (m, 1H), 5.7 (m, 1H).

vi) 2.1 g (12.69 mmol) of (E)-L-(2-butenyl)glycine hydrochloride were suspended in 20 ml of water and 20 ml of dioxan. 8.26 g (98.32 mmol) of sodium hydrogen carbonate and 8.15 g (37.33 mmol) of di-tert-butyl dicarbonate were added and the resulting solution was stirred for overnight. The solution was evaporated to dryness under a vacuum and the residue was partitioned between diethyl ether and saturated aqueous sodium hydrogen carbonate solution. The aqueous phase was acidified with 2M hydrochloric acid while partitioning in ethyl acetate. The organic phase was dried over magnesium sulphate and the solvent was removed by evaporation to give 1.34 g of (E)-N-(tert-butoxycarbonyl)-L-2-(2-butenyl)glycine; ^1H NMR (250 MHz, $CDCl_3$) d: 1.4 (s, 9H), 1.65 (d, 3H), 2.5 (m, 2H), 4.3 (m, 1H), 5.0 (m, 1H), 5.35 (m, 1H), 5.6 (m, 1H).

vii) 1.34 g (5.85 mmol) of (E)-N-(tert-butoxycarbonyl)-L–2-(2-butenyl)glycine were dissolved in 50 ml of anhydrous tetrahydrofuran and the solution was treated in sequence with 0.80 g (8.20 mmol) of N,O-dimethylhydroxylamine hydrochloride, 1.10 g (7.19 mmol) of 1-hydroxybenzotriazole monohydrate, 1.57 g (8.22 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 4 ml (22.96 mmol) of ethyldiisopropylamine. The solution obtained was stirred at room temperature overnight, then washed with saturated sodium hydrogen carbonate solution and with saturated sodium chloride solution and dried over magnesium sulphate. Removal of the solvent by evaporation yielded 1.56 g of N,O-dimethyl (E)-2(S)-(tert-butoxyformamido)-4-hexenohydroxamate as a colourless oil which was used in the next step without purification. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.4 (s, 9H), 1.65 (d, 3H), 2.3 (m, 2H), 3.15 (s, 3H), 3.75 (s, 3H), 4.7 (m, 1H), 5.1 (d, 1H), 5.35 (m, 1H), 5.5 (m, 1H).

viiii) 1.56 g (5.74 mmol) of N,O-dimethyl (E)-2(S)-(tert-butoxyformamido)-4-hexenohydroxamate were dissolved in 10 ml of anhydrous tetrahydrofuran and cooled to 0°C. 4.0 ml of a 1M solution of lithium aluminium hydride in tetrahydrofuran were added and the resulting solution was stirred for 30 minutes. The reaction was quenched by the dropwise addition of saturated potassium hydrogen sulphate solution followed by diethyl ether. The resulting two-phase system was stirred vigorously for 3 minutes. The organic phase was washed with saturated sodium hydrogen carbonate solution followed by saturated sodium chloride solution and dried over anhydrous magnesium sulphate. After removal of the solvent by evaporation the resulting aldehyde was used without purification.

1 g (4.69 mmol) of the aldehyde was dissolved in a saturated solution of hydrogen chloride in methanol and stirred at room temperature for 2 hours. After removal of the solvent by evaporation the dimethyl acetal obtained was used without purification.

0.15 mg (0.16 mmol) of N-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine, 0.033 g (0.22 mmol) of 1-hydroxybenzotriazole monohydrate, 0.047 g (0.25 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.77 g (6.69 mmol) of 4-ethylmorpholine were dissolved in 15 ml of dichloromethane. 0.05 g (0.22 mmol) of the dimethyl acetal dissolved in 5 ml of dichloromethane was added and the resulting solution was stirred at room temperature for 3 days. The mixture was washed with 5% citric acid solution followed by saturated sodium hydrogen carbonate solution and saturated sodium chloride solution and then dried over anhydrous magnesium sulphate. After evaporation of the solvent the crude product was chromatographed on silica gel using 2% methanol in dichloromethane for the elution to give 0.079 g of (E)-N2-[N-[N-[N-[N-(3-tert-butoxycarbonyl)propionyl]-tert-butyl-L-α-aspartyl]-O-tert-butyl-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(S)-(dimethoxymethyl)-3-pentyl]-L-leucinamide as a white solid foam; m/e 1027.9 [M+H-MeOH]+.

Example 31

0.05 g (0.04 mmol) of (Z)-N2-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(S)-(dimethoxymethyl)-3-pentenyl]-L-leucinamide was dissolved in 4 ml of a 1:1 solution of dichloromethane and trifluoroacetic acid and containing 3 drops of water. The solution was stirred at room temperature for 1 hour. After removal of the solvent by evaporation the crude product was triturated using diethyl ether to afford 0.03 g of (Z)-2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-alpha-aspartyl]-L-alpha-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4-hexenai as a white solid; MS: m/e 845.7 $[M+H]^+$.

The starting material was prepared as follows:

i) 25 g (347 mmol) of cis-2-buten-1-ol were dissolved in 750 ml of anhydrous diethyl ether. 7.25 ml of anhydrous pyridine were added and the resulting solution cooled to 0°C. 88.25 ml of phosphorus tribromide was added dropwise and the mixture was stirred for 2 hours at 0°C. The reaction was quenched by pouring the solution onto ice. The organic phase was washed with saturated sodium chloride solution and dried over anhydrous magnesium sulphate. After removal of the solvent by evaporation there was obtained 25.65 g of (Z)-1-bromo-2-butene; ^1H NMR (250 MHz, $CDCl_3$) δ: 1.65 (d, 3H), 3.9 (d, 2H), 5.6 (m, 2H).

ii) 4.37 g (190 mmol) of sodium metal were dissolved in 110 ml of anhydrous ethanol. 41.14 g (189.6 mmol) of diethyl acetamidomalonate dissolved in 270 ml of anhydrous ethanol were added and the mixture was heated under reflux for 10 minutes. 25.65 g (168 mmol) of (Z)-1-bromo-2-butene were added dropwise at room temperature and the mixture was stirred overnight, then evaporated to dryness under vacuum and the residue was partitioned between ethyl acetate and 0.1 M hydrochloric acid. The organic phase was washed with saturated sodium hydrogen carbonate solution followed by saturated sodium chloride solution and dried over anhydrous magnesium sulphate. After removal of the solvent by evaporation the crude product was chromatographed on silica gel using 66% ethyl acetate in petroleum ether as eluent to obtain 44.69 g of diethyl (Z)-2-acetamido-2-(2-butenyl)malonate as a colourless oil; ^1H NMR (250 MHz, $CDCl_3$) δ: 1.2 (t, 6H), 1.6 (d, 3H), 2.0 (s, 3H), 3.1 (d, 2H), 4.2 (q, 4H), 5.1(m, 1H), 5.6 (m, 1H), 6.7 (s, 1H).

iii) 44.69 g (165 mmol) of diethyl (Z)-2-acetamido-2-(2-butenyl)malonate were dissolved in 230 ml of ethanol and a solution of 21.69 g (542 mmol) of sodium hydroxide in water was added. The mixture was stirred for 2 hours at 60°C, evaporated to dryness under a vacuum and the residue was partitioned between diethyl ether and water. The aqueous phase was acidified using 2M hydrochloric acid and extracted with ethyl acetate. The organic phase was dried over magnesium sulphate and the solvent removed by evaporation in a vacuum to give 33.5 g of (Z)-2-acetamido-2-(2-butenyl)malononic acid as a

white solid; ^1H NMR (250 MHz, MeOD) δ: 1.6 (d, 3H), 2.0 (s, 3H), 2.85 (d, 2H), 5.25 (m, 1H), 5.6 (m, 1H).

iv) 16.82 g (78.23 mmol) of (Z)-2-acetamido-2-(2-butenyl)-malononic acid were dissolved in 100 ml of toluene. 34 ml (242 mmol) of triethylamine were added and the mixture was heated under reflux for 1 h, then washed with 1M hydrochloric acid and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried over magnesium sulphate and the solvent was removed under a vacuum to give 9.4 g of (Z)-N-acetyl-DL-2-(2-butenyl)glycine as a white solid; ^1H NMR (250 MHz, MeOD) δ: 1.6 (d, 3H), 2.0 (s, 3H), 2.5 (m, 2H), 4.4 (m, 1H), 5.4 (m, 1H), 5.6 (m, 1H).

v) 9.4 g (54.97 mmol) of (Z)-N-acetyl-DL-2-(2-butenyl)-glycine were dissolved in 100 ml of water and the pH was adjusted to 7.8 with ammonia solution. 0.09 g of acylase I extracted from porcine kidney, and 0.042 g (0.3 mmol) of cobalt (II) chloride were added and the resulting reaction mixture was stirred at 37°C overnight. The pH was adjusted to 7.8 using ammonia solution. The mixture was stirred at 37°C overnight and was then heated at 80°C for 30 minutes and was then acidified to pH 1 using 2M hydrochloric acid. The solution was acidified to pH 1 using 2M hydrochloric acid and then heated at 80°C for 30 minutes. The solvent was removed by evaporation under a vacuum and the crude product obtained purified by trituration using ethyl acetate to yield 5.86 g of (Z)-L-2-(2-butenyl)glycine hydrochloride; ^1H NMR (250 MHz, D_2O) δ: 1.6 (d, 3H), 2.7 (t, 2H), 4.1 (t, 1H), 5.3 (m, 1H), 5.8 (m, 1H).

vi) 2.9 g (17.52 mmol) of (Z)-L-2-(2-butenyl)glycine hydrochloride were suspended in 25 ml of water and 25 ml of dioxan. 11.4 g (136 mmol) of sodium hydrogencarbonate and 8.49 g (38.94 mmol) of di-tert-butyl dicarbonate were added and the resulting solution was stirred for 48 hours. The solution was evaporated to dryness under a vacuum and the residue was partitioned between diethyl ether and saturated aqueous sodium hydrogen carbonate solution. The aqueous phase was acidified

using 2M hydrochloric acid whilst being partitioned with ethyl acetate. The organic phase was dried over magnesium sulphate and the solvent removed by evaporation to give 2.26 g of (Z)-N-(tert-butoxycarbonyl)-L-2-(2-butenyl)glycine; ^1H NMR (250 MHz, $CDCl_3$) δ: 1.4 (s, 9H), 1.6 (d, 3H), 2.6 (m, 2H), 4.4 (m, 1H), 5.05 (m, 1H), 5.3 (m, 1H), 5.6 (m, 1H).

vii) 2.26 g (9.87 mmol) of (Z)-N-(tert-butoxycarbonyl)-L-2-(2-butenyl)glycine were dissolved in 50 ml of anhydrous tetrahydrofuran. 1.15 g (11.79 mmol) of N,O-dimethylhydroxylamine hydrochloride, 1.6 g (10.46 mmol) of 1- hydroxybenzotriazole monohydrate, 2.27 g (11.88 mmol) of 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride and 5.8 ml of ethyldiisopropylamine were added and the resulting solution was stirred at room temperature overnight. The solution was washed with saturated sodium hydrogen carbonate solution followed by saturated sodium chloride solution and then dried over anhydrous magnesium sulphate. Removal of the solvent by evaporation yielded 2.46 g of N,O-dimethyl (Z)-2(S)-(tert-butoxyformamido)-4-hexenohydroxamate as a colourless oil; ^1H NMR (250 MHz, $CDCl_3$) δ: 1.4 (s, 9H), 1.6 (d, 3H), 2.35 (m, 1H), 2.5 (m, 1H), 3.2 (s, 3H), 3.75 (s, 3H), 4.7 (m, 1H), 5.2 (d, 1H), 5.35 (m, 1H), 5.6 (m, 1H).

viii) 1.01 g (3.71 mmol) of N,O-dimethyl (Z)-2(S)-(tert-butoxy-formamido)-4-hexenohydroxamate were dissolved in 10 ml of anhydrous tetrahydrofuran and cooled to 0°C. 2.6 ml of a 1M solution of lithium aluminium hydride in tetrahydrofuran were added and the resulting solution was stirred for 30 minutes. The reaction was quenched by the dropwise addition 15 ml of saturated potassium hydrogen sulphate solution followed by 30 ml of diethyl ether. The resulting two-phase system was stirred vigorously for one hour. The organic phase was washed with saturated sodium hydrogen carbonate solution followed by saturated sodium chloride solution and dried over magnesium sulphate. After removal of the solvent by evaporation the aldehyde was used without further purification. 0.79 g (3.71 mmol) of the aldehyde was dissolved in a saturated solution of hydrogen chloride in 10 ml of methanol and stirred at room temperature for 2 hours. After removal of the solvent by evaporation the

dimethylacetal obtained was used without purification

0.15 g (0.16 mmol) of N-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine, 0.033 g (0.22 mmol) of 1-hydroxybenzotriazole mono hydrate, 0.047 g (0.25 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 0.77 g (6.69 mmol) of 4-ethylmorpholine were dissolved in 15 ml of dichloromethane. 0.05 g (0.22 mmol) of the foregoing dimethyl acetal dissolved in 5 ml of dichloromethane was added and the resulting solution was stirred at room temperature for 3 days. The solution was washed with 5% citric acid solution followed by saturated sodium hydrogen carbonate solution and saturated sodium chloride solution and then dried over magnesium sulphate. After removal of the solvent by evaporation the crude product was chromatographed on silica gel using 2% methanol in dichloromethane for the elution to give 0.092 g of (Z)-N2-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(S)-(dimethoxymethyl)-3-pentenyl]-L-leucinamide, as a white solid foam; MS: m/e 1027.9 $[M + H - MeOH]^+$.

Example 32

In an analogous manner to that described in Example 10, but using N-(tert-butoxycarbonyl)-3-(2-furyl)-L-alanine in place of N-(tert-butoxycarbonyl)-L-allylglycine there was obtained 2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-3-(2-furyl)propionaldehyde; MS: m/e 871.4 $[M+H]^+$.

The starting material was prepared in an analogous manner to that described in Example 10 via the following intermediates:

i) N,O-Dimethyl 2(S)-(tert-butoxyformamido)-2-(2-furyl)-propionohydroxamate; ^1H NMR (250 MHz, $CDCl_3$) δ: 1.4 (s, 9H), 3.0 (m, 2H), 3.2 (s, 3H), 3.7 (s, 3H), 4.9 (m, 1H), 5.3 (br. d, 1H), 6.1 (br. s, 1H), 6.3 (br. s, 1H), 7.3 (br. s, 1H).

ii) N2-[N-[N-[N-[N-[3-(tert-Butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[2-(2-furyl)-1(S)-(dimethoxymethyl)ethyl]-L-leucinamide; used directly in the next step.

Example 33

In an analogous manner to that described in Example 10, but using N-(tert-butoxycarbonyl)-L-norvaline in place of N-(tert-butoxycarbonyl)-L-allylglycine there was obtained 2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-valeraldehyde; MS: m/e 833.4 $[M+H]^+$.

The starting material was prepared in an analogous manner to that described in Example 10 via the following intermediates:

N,O-Dimethyl 2(S)-(tert-butoxyformamido)valerohydroxamate; ^1H NMR (250 MHz, $CDCl_3$) δ: 0.8 (m, 3H), 1.2-1.7 (m, 4H), 1.4 (s, 9H), 3.1 (s, 3H), 3.7 (s, 3H), 4.6 (m, 1H), 5.1 (br. d, 1H).

N2-[N-[N-[N-[N-[3-(tert-Butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(S)-(dimethoxymethyl)-butyl]-L-leucinamide; MS: m/e 1069.6 $[M+Na]^+$.

Example 34

In an analogous manner to that described in Example 10, but using N-(tert-butoxycarbonyl)-L-butylglycine in place of N-(tert-butoxycarbonyl)-L-allylglycine there was obtained 2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-hexanal; MS: m/e 847.4 [M+H]+.

The starting material was prepared in an analogous manner to that described in example 10 via the following intermediates:

i) N,O-Dimethyl 2(S)-(tert-butoxyformamido)hexanohydroxamate; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.9 (m, 3H), 1.2-1.8 (m, 6H), 1.4 (s, 9H), 3.2 (s, 3H), 3.7 (s, 3H), 4.6 (m, 1H), 5.1 (br. d, 1H).

ii) N2-[N-[N-[N-[N-[3-(tert-Butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(S)-(dimethoxymethyl)-pentyl]-L-leucinamide; MS: m/e 1083 $[M + Na]^+$.

Example 35

In an analogous manner to that described in Example 10, but using DL-hexylglycine in place of L-allylglycine hydrochloride there was obtained 2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]octanal; MS: m/e 875.5 $[M+H]^+$.

The starting material was prepared in an analogous manner to that described in Example 10 via the following intermediates:

i) 2(RS)-(tert-Butoxyformamido)octanoic acid; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.9 (m, 3H), 1.2-1.9 (m, 10H), 1.4 (s, 9H), 4.3 (m, 1H), 5.0 (br. d, 1H)

ii) N,O-Dimethyl 2(RS)-(tert-butoxyformamido)octanohydroxamate; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.9 (m, 3H), 1.2-1.8 (m, 10H), 1.4 (s, 9H), 3.2 (s, 3H), 3.7 (s, 3H) 4.6 (m, 1H), 5.1 (br. d, 1H)

iii) N2-[N-[N-[N-[N-[3-(tert-Butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(RS)-(dimethoxymethyl)-heptyl]-L-leucinamide; MS: m/e 1111.6 $[M + Na]^+$.

Example 36

In an analogous manner to that described in Example 10, but using 2(S)-amino-5-methylhexanoic acid in place of L-allylglycine hydrochloride there was obtained 2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-5-methylhexanal; MS: m/e 861.3 $[M+H]^+$

The starting material was prepared in an analogous manner to that described in Example 10 via the following intermediates:

i) 2(S)-(tert-Butoxyformamido)-5-methylhexanoic acid; 1H NMR (250 MHz, $CDCl_3$) δ: 0.9 (d, 6H), 1.2 (m, 2H), 1.4 (s, 9H), 1.5 (m, 1H), 1.7 (m, 1H), 1.9 (m, 1H), 4.3 (m, 1H), 4.9 (br. d, 1H).

ii) N,O-Dimethyl 2(S)-(tert-butoxyformamido)-5-methylhexanohydroxamate; 1H NMR (250 MHz, $CDCl_3$) δ: 0.85 (d, 3H), 0.9 (d, 3H), 1.2 (m, 2H), 1.4 (s, 9H), 1.4-1.8 (m, 3H), 3.2 (s, 3H), 3.8 (s, 3H), 4.6 (m, 1H), 5.1 (br. d, 1H).

iii) N2-[N-[N-[N-[N-[3-(tert-Butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(S)-(dimethoxymethyl)-4-methylpentyl]-L-leucinamide; MS: m/e 1043.8 $[M+H-MeOH]^+$.

Example 37

In an analogous manner to that described in Example 10, but using 2(S)-amino-5-hexenoic acid in place of L-allylglycine hydrochloride there was obtained 2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-5-hexenal; MS: m/e 845.3 $[M+H]^+$.

The starting material was prepared in an analogous manner to that described in Example 10 via the following intermediates:

i) 2(S)-tert-Butoxyformamido)-5-hexenoic acid; 1H NMR (250 MHz, $CDCl_3$) δ: 1.4 (s, 9H), 1.8 (m, 1H), 1.95 (m, 1H), 2.2 (m, 2H), 4.3 (m, 1H), 5.0 (m, 3H), 5.8 (m, 1H).

ii) N,O-Dimethyl 2(S)-(tert-butoxyformamido)-5-hexeno-hydroxamate; 1H NMR (250 MHz, $CDCl_3$) δ: 1.4(s, 9H), 1.6-1.8 (m, 2H), 2.1 (m, 2H), 3.2 (s, 3H), 3.7 (s, 3H) 4.7 (m, 1H), 5.0 (m, 3H), 5.8 (m, 1H).

iii) N2-[N-[N-[N-[N-[3-(tert-Butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(S)-(dimethoxymethyl)-4-pentenyl]-L-leucinamide; MS: m/e 1081.6 [M + Na]+.

Example 38

In an analogous manner to that described in Example 10, but using 2(S)-amino-5-hexynoic acid in place of L-allylglycine hydrochloride there was obtained 2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-5-hexynal; MS: m/e 843.3 $[M+H]^+$.

The starting material was prepared in an analogous manner to that described in Example 10 via the following intermediates:

i) 2(S)-(tert-Butoxyformamido)-5-hexynoic acid; 1H NMR (250 MHz, MeOD) δ: 1.4 (s, 9H), 1.8 (m, 1H), 2.0 (m, 1H), 2.3 (m, 3H), 4.2 (m, 1H).

ii) N,O-Dimethyl 2(S)-(tert-butoxyformamido)-5-hexyno-hydroxamate; 1H NMR (250 MHz, MeOD) δ: 1.4 (s, 9H), 1.7 (m, 1H), 1.9 (m, 1H), 2.3 (m, 3H), 3.2 (s, 3H), 3.8 (s, 3H), 4.7 (m, 1H)

iii) N2-[N-[N-[N-[N-[3-(tert-Butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(S)-(dimethoxymethyl)-4-pentynyl]-L-leucinamide; MS: m/e 1079.5 $[M+Na]^+$

Example 39

In an analogous manner to that described in Example 10, but using N-(tert-butoxycarbonyl)-L-methionine in place of N-(tert-butoxycarbonyl)-L-allylglycine there was obtained 2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4-(methylthio)butyraldehyde; MS: m/e 865.3 $[M+H]^+$.

The starting material was prepared in an analogous manner to that described in Example 10 via the following intermediates:

i) N,O-Dimethyl 2(S)-(tert-butoxyformamido)-4-(methylthio)butyrohydroxamate; 1H NMR (250 MHz, $CDCl_3$) δ: 1.4 (s, 9H), 1.75 (m, 1H), 2.0 (m, 1H), 2.05 (s, 3H), 2.5 (m, 2H), 3.2 (s, 3H), 3.75 (s, 3H), 4.7 (m, 1H), 5.2 (m, 1H).

ii) N2-[N-[N-[N-[N-[3-(tert-Butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(S)-(dimethoxymethyl)-2-(methylthio)propyl]-L-leucinamide; MS: m/e 1047.5 $[M+H-MeOH]^+$.

Example 40

In an analogous manner to that described in Example 10, but using S-(3-phenylpropyl)-L-cysteine in place of L-allylglycine hydrochloride there was obtained 2(R)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-2-[3-(phenyl)propylthio]propionaldehyde; MS: m/e 955.4 $[M+H]^+$.

The starting material was prepared in an analogous manner to that described in Example 10 via the following intermediates:

i) N-(tert-Butoxycarbonyl)-S-(3-phenylpropyl)-L-cysteine; 1H NMR (250 MHz, $CDCl_3$) δ: 1.4 (s, 9H), 1.9 (m, 2H), 2.55 (t, 2H), 2.7 (t, 2H), 3.0 (m, 2H), 4.5 (m, 1H), 5.4 (m, 1H), 7.2 (m, 5H).

ii) N,O-Dimethyl 2(S)-(tert-butoxyformamido)-3-(3-phenylpropylthio)propionohydroxamate; 1H NMR (250 MHz, $CDCl_3$) δ: 1.4 (s, 9H), 1.9 (m, 2H), 2.5 (t, 2H), 2.7 (t, 2H), 2.8 (m, 2H), 3.2 (s, 3H), 3.7 (s, 3H), 4.8 (m, 1H), 5.3 (m, 1H), 7.2 (m, 5H).

iii) N2-[N-[N-[N-[N-[3-(tert-Butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(R)-(dimethoxymethyl)-2-(3-phenylpropylthio)ethyl]-L-leucinamide; MS: m/e 1191.8 $[M+Na]^+$.

Example 41

In an analogous manner to that described in Example 1, but using N,O-Dimethyl 2(S)-(tert-butoxyformamido)hexanohydroxamate in place of N,O-Dimethyl 2(S)-(tert-butoxyformamido)-butyrohydroxamate and N-(9-fluorenylmethoxycarbonyl)-D-valine in place of N-(9-fluorenylmethoxycarbonyl)-O-tert-butyl-L-α-glutamic acid there was obtained 2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-D-valyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]hexanal; MS: m/e 817.4 $[M+H]^+$.

The starting material was prepared in an analogous manner to that described in Example 1 via the following intermediates:

i) N-[N-[N-[N-[(9-Fluorenyl)methoxycarbonyl]-D-valyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine benzyl ester; MS: m/e 817.4 $[M+H]^+$.

ii) N-[N-[N-[N-[N-[(9-Fluorenyl)methoxycarbonyl]-O-tert-butyl-L-α-aspartyl]-D-valyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine benzyl ester; MS: m/e 988.4 $[M+H]^+$.

iii) N-[N-[N-[N-[N-[3-(tert-Butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-D-valyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine benzyl ester; MS: m/e 922.5 $[M+H]^+$.

iv) N-[N-[N-[N-[N-[3-(tert-Butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-D-valyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine; MS: m/e 832.5 $[M+H]^+$.

v) N2-[N-[N-[N-[N-[3-(tert-Butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-D-valyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(S)-(dimethoxymethyl)pentyl]-L-leucinamide; MS: m/e 997.5 $[M+Na]^+$.

Example 42

In an analogous manner to that described in Example 1, but using N,O-dimethyl 2(S)-(tert-butoxyformamido)hexanohydroxamate in place of N,O-dimethyl 2(S)-(tert-butoxyformamido)-butyrohydroxamate, using N-(9-fluorenylmethoxycarbonyl)-D-valine in place of N-(9-fluorenylmethoxycarbonyl)-O-tert-butyl-L-α-glutamic acid and using O-tert-butyl-N-[(9-florenyl)-methoxycarbonyl]-L-serine in place of N-(9-fluorenylmethoxy-carbonyl)-O-tert-butyl-L-α-aspartic acid there was obtained 2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-seryl]-D-valyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-hexanal; MS: m/e 789.3 $[M+H]^+$.

The starting material was prepared in an analogous manner to that described in Example 1 via the following intermediates:

i) N-[N-[N-[N-[N-[(9-Fluorenyl)methoxycarbonyl]-O-tert-butyl-L-seryl]-D-valyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine benzyl ester; MS: m/e 960.4 $[M+H]^+$.

ii) N-[N-[N-[N-[N-[3-(tert-Butoxycarbonyl)propionyl]-O-tert-butyl-L-seryl]-D-valyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine benzyl ester; MS: m/e 894.5 $[M+H]^+$.

iii) N-[N-[N-[N-[N-[3-(tert-Butoxycarbonyl)propionyl]-O-tert-butyl-L-seryl]-D-valyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine; MS: m/e 804.4 $[M+H]^+$.

iv) N2-[N-[N-[N-[N-[3-(tert-Butoxycarbonyl)propionyl]-O-tert-butyl-L-seryl]-D-valyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(S)-(dimethoxymethyl)pentyl]-L-leucinamide; MS: m/e 969.7 [M+Na]+.

Example 43

In an analogous manner to that described in Example 1, but using N,O-dimethyl 2(S)-(tert-butoxyformamido)hexanohydroxamate in place of N,O-dimethyl 2(S)-(tert-butoxyformamido)-butyrohydroxamate using N-(9-fluorenylmethoxycarbonyl)-D-valine in place of N-(9-fluorenylmethoxycarbonyl)-O-tert-butyl-L-α-glutamic acid, using O-tert-butyl-N-[(9-florenyl)methoxy-carbonyl]-L-serine in place of N-(9-fluorenylmethoxycarbonyl)-O-tert-butyl-L-α-aspartic acid and using acetic anhydride in place of tert-butyl hydrogen succinate there was obtained 2(S)-[[N-[N-[N-[N-(N-acetyl-L-seryl)-D-valyl]-2-methyl-L-phenyl-alanyl]-3-methyl-L-valyl]-L-leucyl]amino]hexanal; MS: m/e 731.3 [M+H]+.

The starting material was prepared in an analogous manner to that described in Example 1 via the following intermediates:

i) N-[N-[N-[N-(N-acetyl-O-tert-butyl-L-seryl)-D-valyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine; MS: m/e 690.4 [M+H]+.

ii) N2-[N-[N-[N-(N-acetyl-O-tert-butyl-L-seryl)-D-valyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(S)-(dimethoxy-methyl)pentyl]-L-leucinamide; MS: m/e 833.5 [M+H]+.

The reaction with acetic anhydride was carried out as follows:

0.5ml of N-ethylmorpholine and 0.37 ml of acetic anhydride were added in sequence to a solution of 1.95 g of N-[N-[N-[N-(O-tert-butyl-L-seryl)-D-valyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine benzyl ester in 70 ml of anhydrous

dichloromethane. The mixture was stirred at room temperature for 1 hour and was then washed in sequence with 5% aqueous citric acid solution, saturated aqueous sodium bicarbonate solution and saturated brine. The organic phase was dried over anhydrous magnesium sulphate and evaporated. Chromatography of the residue on silica using 5% methanol in dichloromethane for the elution gave afforded 1.45 g of N-[N-[N-[N-(N-acetyl-O-tert-butyl-L-seryl)-D-valyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine benzyl ester; MS: m/e 780.6 [M+H]+.

Example 44

59 mg (0.058 mmol) of N1-[4-bromo-1(RS)-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)butyl]-N2-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methylL-phenylalanyl]-3-methyl-L-valyl]-L-leucinamide were dissolved in 3 ml of trifluoroacetic acid and 3 ml of dichloromethane. 5 drops of water were added and the solution was stirred at room temperature for 3 hours. The solution was diluted with toluene and evaporated. The residue was triturated with diethyl ether and the resulting solid was filtered off and dried and then redissolved in 5 ml of trifluoroacetic acid and 5 ml of dichloromethane. The solution was stirred at room temperature for 3 hours and then diluted with toluene and evaporated. The residue was triturated with diethyl ether and the solid obtained was filtered off and dried to give 30 mg of 4-bromo-1(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methylL-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]butylboronic acid in the form of a solid; MS: m/e 911.3 $[M+H-H_2O]^+$.

The starting material was prepared as follows:

i) 1.7 ml (1.7 mmol) of 1M lithium bis(trimethylsilyl)amide in tetrahydrofuran were added dropwise to a solution of 0.5 g (1.7 mmol) of 2-(4-bromo-1(RS)-chlorobutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (prepared according to EP-A-O 293 881) in 5 ml of tetrahydrofuran under nitrogen at -78°C.

The solution was then stirred overnight at room temperature. The solvent was removed by evaporation and the residue was taken up in diethyl ether. Insoluble material was removed by filtration and the solvent was removed by evaporation to give 0.63 g of product which was immediately redissolved in diethyl ether and cooled to 0°C. 0.34 ml 0.34 ml (5.0 mmol) of trifluoroacetic acid was added and the solution was stirred at 0°C for 30 minutes. The solution was evaporated and the residue was evaporated with toluene to give 0.58 g of α-(RS)-3-bromopropyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-methylamine trifluoroacetate (1:1) as a brown oil which was used in the next step without purification.

ii) 0.20 g (0.22 mmol) of N-[N-[N-[N-[N-(tert-butoxy-carbonyl)-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine was dissolved in 2 ml of dimethylformamide and 6 ml of dichloromethane. 0.2 ml (1.52 mmol) of N-methylmorpholine was added and the solution was cooled to -10°C under a nitrogen atmosphere. 44 mg (0.3 mmol) of isobutyl chloroformate were added and the solution was stirred for 15 minutes at -10°C. 0.3 g (0.66 mmol) of a(RS)-3-bromopropyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-methylamine trifluoroacetate (1:1) was added and the mixture was stirred at room temperature for 5 hours. Dichloromethane was added and the solution was extracted with 2M hyrochloric acid and water and then dried over anhydrous sodium sulphate. After evaporation there was obtained 0.122 g of N2-[N-[N-[N-[N-(tert-butoxycarbonyl)-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenyl-alanyl]-3-methyl-L-methyl-L-valyl]-N1-[4-bromo-1(RS)-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl]-L-leucinamide in the form of a solid; MS: m/e 1079.5 $[M+H-100]^+$.

iii) 115 mg (0.098 mmol) of N2-[N-[N-[N-[N-(tert-butoxy-carbonyl)-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-a-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[4-bromo-1(RS)-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-butyl]-L-leucinamide were dissolved in 3 ml of trifluoroacetic

acid and 3 ml of dichloromethane. 5 drops of water were added and the solution was stirred at room temperature for 3 hours. The solution was diluted with toluene and evaporated. The residue was triturated with ether and the resulting solid was filtered off and dried to give 72 mg of N1-[4-bromo-1(RS)-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)butyl]-N2-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-methyl-valyl]-L-leucinamide as a white solid; MS: m/e 911.3 [M+H-100]+

Example 45

In an analogous manner to that described in Example 23, but replacing N-[(9-fluorenyl)methoxycarbonyl]-O-tert-butyl-L-tyrosine with N-[(9-fluorenyl)methoxycarbonyl]-O-tert-butyl-L-aspartic acid and replacing N-[(9-fluorenyl)methoxycarbonyl]-3-methyl-L-valine with N-[(9-fluorenyl)methoxycarbonyl]-L-2-cyclohexylglycine there was obtained 1(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methylL-phenylalanyl]-L-2-cyclohexylglycyl]-L-leucyl]amino]propylboronic acid as a white solid; MS: m/e 843.4 $[M+H-H_2O]^+$.

Example 46

In an analogous manner to that described in Example 23, but replacing N-[(9-fluorenyl)methoxycarbonyl]-O-tert-butyl-L-tyrosine with N-[(9-fluorenyl)methoxycarbonyl]-O-tert-butyl-L-aspartic acid and replacing N-[(9-fluorenyl)methoxycarbonyl-2-methyl-L-phenylalanine with N-[(9-fluorenyl)methoxycarbonyl]-L-2-cyclohexylglycine there was obtained 1(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-L-2-cyclohexylglycyl]-3-methyl-L-valyl]-L-leucyl]amino]propylboronic acid as a white solid; MS: m/e 795.5 $[M+H-H_2O]^+$.

Example 47

In an analogous manner to Example 4, by replacing N-[(9-fluorenyl)methoxycarbonyl]-3-(2-naphthyl)-D-alanine with N-[(9-

fluorenyl)methoxycarbonyl]-3-cyclohexyl-L-alanine there was obtained 2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-3-cyclohexyl-L-alanyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde as a white solid; MS m/e 897.6 [M+H].

Example 48

In an analogous manner to Example 4, by replacing N-[(9-fluorenyl)methoxycarbonyl]-3-(2-naphthyl)-D-alanine with N-[(9-fluorenyl)methoxycarbonyl]-D-valine and replacing N-[(9-fluorenyl)methoxycarbonyl]-O-t-butyl-L-α-aspartic acid with N-[(9-fluorenyl)methoxycarbonyl]-O-t-butyl-L-serine there was obtained 2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-seryl]-D-valyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]-amino]-4,4,4-trifluorobutyraldehyde as a white solid; MS: m/e 815.5 [M+H].

Example 49

In an analogous manner to Example 4, by replacing N-[(9-flurenyl)methoxycarbonyl]-3-(2-naphthyl)-D-alanine with [(9-fluorenyl)methoxycarbonyl]-D-norleucine there was obtained 2(RS)-[[N-[N-[N-[N-[N-(3-carbonylpropionyl)-L-α-aspartyl]-D-norleucyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde as a white solid;MS: m/e 857.4 [M+H].

Example 50

In an analogous manner to Example 4, by replacing N-[(9-fluorenyl)methoxycarbonyl]-3-(2-naphthyl)-D-alanine with N-[(9-fluorenyl)methoxycarbonyl]-D-norvaline there was obtained 2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-D-norvalyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]-amino]-4,4,4-trifluorobutyraldehyde as a white solid; MS: m/e 843.4 [M+H].

Example 51

In an analogous manner to Example 4, by replacing N-[(9-fluorenyl)methoxycarbonyl]-3-(2-naphthyl)-D-alanine with N-[(9-fluorenyl)methoxycarbonyl]-D-2-cyclohexylglycine there was obtained 2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-D-2-cyclohexylglycyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde as a white solid, MS: m/e 897.4 [M+H].

Example 52

In an analogous manner to Example 4, by replacing N-[(9-fluorenyl)methoxycarbonyl]-3-(2-naphthyl)-D-alanine with N-[(9-fluorenyl)methoxycarbonyl]-4-nitro-D-phenylalanine there was obtained 2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-4-nitro-D-phenylalanyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde as a white solid; MS: m/e 936.3 [M+H].

Example 53

In an analogous manner to Example 4, by replacing N-[(9-fluorenyl)methoxycarbonyl]-3-methyl-L-valine with N-[(9-fluorenyl)methoxycarbonyl]-L-2-cyclohexylglycine and by replacing N-[(9-fluorenyl)methoxycarbonyl]-3-(2-naphthyl)-D-alanine with N-[(9-fluorenyl)methoxycarbonyl]-O-tert-butyl-L-α-glutamic acid there was obtained 2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-L-2-cyclohexylglycyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde as a white solid; MS: m/e 899.5 [M+H].

Example 54

In an analogous manner to Example 4, by replacing N-[(9-methoxycarbonyl]-3-(2-methylphenyl)-L-alanine with N-[(9-methoxycarbonyl]-L-2-cyclohexylglycine and by replacing N-[(9-fluorenyl)methoxycarbonyl]-3-(2-naphthyl)-D-alanine with N-[(9-

fluorenyl)methoxycarbonyl]-O-t-butyl-L-α-glutamic acid there was obtained 2(RS)-[[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-L-2-cyclohexylglycyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde as a white solid; MS: m/e 851.4 [M+H].

Example 55

In an analogous manner to Example 4, by replacing N-[(9-fluorenyl)methoxycarbonyl]-3-(2-naphthyl)-D-alanine with N-[(9-fluorenyl)methoxycarbonyl]-O-t-butyl-L-α-glutamic acid and by replacing tert-butyl hydrogen succinate with 3-acetamidobenzoic acid there was obtained 2(RS)-[[N-[N-[N-[N-[N-(3-acetamido-benzoyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino-4,4,4-trifluororbutyraldehyde as a white solid; MS: m/e 934.4 [M+H].

Example 56

In an analogous manner to Example 4, by replacing N-[(9-fluorenyl)methoxycarbonyl]-3-(2-naphthyl)-D-alanine with N-[(9-fluorenyl)methoxycarbonyl]-O-t-butyl-L-α-glutamic acid and by rep[lacing tert-butyl hydrogen succinate with 4-acetamido-3-nitrobenzoic acid there was obtained 2(RS)-[[N-[N-[N-[N-[N-(4-acetamido-3-nitrobenzoyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde as a white solid; MS: m/e 979.4 [M+H].

Example 57

In an analogous manner to Example 4, by replacing N-[(9-fluorenyl)methoxycarbonyl]-3-(2-naphthyl)-D-alanine with N-[(9-fluorenyl)methoxycarbonyl]-O-tert-butyl-L-α-glutamic acid and by replacing tert-butyl hydrogen succinate with 4-acetamidobenzoic acid there was obtained 2(RS)-[[N-[N-[N-[N-[N-(4-acetamidobenzoyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde as a white solid; MS: m/e 934.4 [M+H].

Example 58

In an analogous manner to Example 4, by replacing N-[(9-fluorenyl)methoxycarbonyl]-3-(2-naphthyl)-D-alanine with N-[(9-fluorenyl)methoxycarbonyl]-O-tert-L-α-glutamic acid and by replacing tert-butyl hydrogen succinate with 3,5-dichlorobenzoic acid there was obtained 2(RS)-[[N-[N-[N-[N-[N-(3,5-dichlorobenzoyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde as a white solid; MS: m/e 945.3 [M+H].

Example 59

0.78 g of 0.235 mmol/g 5-[2-[1(RS)-[[N-[(9-fluorenyl)-methoxycarbonyl]-L-leucyl]amino]propyl]-4(RS),5,5-trimethyl-1,3,2-dioxoborolan-4-yl]-3(RS)-methyl-N-[α(RS)-(4-methyl-phenyl)benzyl]valeramide-polystyrene conjugate was swollen in dimethylformamide for 20 minutes and then suspended and agitated in dimethylformamide/piperidine (4:1). After 5 minutes the resin was drained and then resuspended in and agitated with dimethylformamide/ piperidine (4:1) for a further five minutes. The resin was then drained and washed five times with dimethylformamide.

The resin was then suspended in a solution of 0.4 g, 1.08 mmol of N-[(9-fluorenyl)methoxycarbonyl]-3-methyl-L-valine in dimethylformamide and then a mixture of 0.42 g (1.08 mmol) 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate and 0.25 ml (2.2 mmol) of N-methylmorpholine dissolved in dimethylformamide was added. After agitating for 40 minutes the resin was drained and washed five times with dimethylformamide.

The resin was resuspended in and agitated with dimethylformamide/piperidine (4:1). After 5 minutes the resin was drained, resuspended in and agitated with dimethylformamide/ piperidine (4:1) for a further 5 minutes. Then the resin was

drained and washed five times with dimethyl formamide.

The resin was then suspended in a solution of 0.44 g (1.08 mmol) of N-[(9-fluorenyl)methoxycarbonyl]-3-(2-methylphenyl)-L-alanine in dimethylformamide and then a mixture of 0.42g 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate and 0.25 ml (2.2 mmol) of N-methylmorpholine dissolved in dimethylformamide was added. After agitating for 40 minutes the resin was drained and washed five times with dimethylformamide.

The resin was resuspended in and agitated with dimethylformamide/piperidine (4:1). After 5 minutes the resin was drained, resuspended in and agitated with dimethylformamide/piperidine (4:1) for a further 5 minutes. Then the resin was drained and washed five times with dimethyl formamide.

The resin was then suspended in a solution of 0.37 g (1.08 mmol) of N-[(9-fluorenyl)methoxycarbonyl]-D-valine in dimethylformamide and then a mixture of 0.42 g of 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate and 0.25 ml (2.2 mmol) of N-methylmorpholine dissolved in dimethylformamide was added. After agitating for 40 minutes the resin was drained and washed five times with dimethylformamide.

The resin was resuspended in and agitated with 0.7 ml of dimethylformamide/piperidine (4:1). After 5 minutes the resin was drained, resuspended in and agitated with dimethylformamide/piperidine (4:1) for a further 5 minutes. Then, the resin was drained and washed five times with 1 ml of dimethylformamide.

98 mg of this resin were then suspended in a solution of 0.06 g (0.19 mmol) of N-(benzyloxycarbonyl)-O-tert-butyl-L-α-aspartic acid in dimethylformamide and then a mixture of 0.06 g (0.19 mmol) of 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate and 0.1 ml (0.88 mmol) of N-methyl-

morpholine dissolved in dimethylformamide was added. After agitating for 40 minutes the resin was drained and washed three times with dimethylformamide, three times with ethyl acetate and three times with dichloromethane.

1 ml of dichloromethane was added to the resin which was then treated with 3 ml of a 9:1 mixture of trifluoroacetic acid and water and then agitated for 30 minutes. The resin was then filtered off and washed with dichloromethane. The filtrate and washings were combined and evaporated and then co-evaporated with toluene. The residue was triturated with diethyl ether and dried. There were obtained 12 mg of 1(RS)-[[N-[N-[N-[N-[N-(benzyloxycarbonyl)-L-α-aspartyl]-D-valyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]propylboronic acid; MS: m/e 821.4 $[M+H-H_2O]^+$.

Example 60

200 mg (0.18 mmol) of N2-[N-[N-[N-[N-(tert-butoxycarbonyl)-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[4-fluoro-1(RS)-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl]-L-leucinamide were dissolved in 4.75 ml of trifluoroacetic acid and 0.25 ml of water. 2 ml of dichloromethane were added and the solution was stirred at room temperature for 3 hours. The solution was diluted with toluene and evaporated. The residue was triturated with diethyl ether and the resulting solid was filtered off and dried to give 95 mg of 4-fluoro-1(RS)-[[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]-amino]butylboronic acid; MS: m/e 849.4 $[M+H-H_2O]^+$

The starting material was prepared as follows:

i) 2.5 ml (25 mmol) of borane-dimethyl sulphide (1:1) complex were dissolved in 50 ml of dimethoxyethane and the solution was cooled to 0^oC under nitrogen. 5.3 ml (52.5 mmol) of cyclohexene were then added. The solution was stirred at 0^oC

for 15 minutes, then at room temperature for 1 hour and then cooled to -10°C. 1.6 g (27 mmol) of 3-fluoropropene were condensed and then added to the foregoing solution which was then stirred at room temperature under a dry ice condenser. After 1 hour the condenser was removed and stirring was continued for a further 1 hour. 3.9 g (52 mmol) of trimethylamine N-oxide were added and the solution was stirred for 1 hour. 3.1 g (26.3 mmol) of 2,3-dimethyl-2,3-butanediol were added and the solution was stirred for 16 hours. The solution was evaporated and the residue was distilled. The distillate boiling at 35-65°C/1mm Hg was collected and purified by chromatography on silica gel using diethyl ether/ hexane (1:9) for the elution to give 1.67 g of 4,4,5,5-tetramethyl-2-(3-fluoropropyl)-1,3,2-dioxaborolane as a colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.75-0.85 (m, 2H), 1.25 (s, 12H), 1.7-1.9 (m, 2H), 4.28 (t, 1H), 4.48 (t, 1H).

ii) 1.3 ml (8.8 mmol) of diisopropylamine and 5.5 ml (8.8 mmol) of butyllithium in hexane were added to 7 ml of tetrahydrofuran at -78°C. The cooled solution was added to a solution of 1.65 g (8.8 mmol) of 4,4,5,5-tetramethyl-2-(3-fluoropropyl)-1,3,2-dioxaborolane in 0.7 ml of dichloromethane, 15 ml of cyclohexane and 8 ml of tetrahydrofuran at -20°C under nitrogen. The solution was then stirred for 16 hours while slowly warming to room temperature. The solution was partitioned between 2M hydrochloric acid, brine and ethyl acetate, and the aqueous layer was extracted with ethyl acetate. The organic extracts were combined, washed with brine and dried over sodium sulphate. After evaporation the residue was purified by chromatography on silica gel using diethyl ether/hexane (1:9) for the elution to give 1.0 g of 2-(4-fluoro-1(RS)-chlorobutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as a colourless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.75-0.85 (m, 2H), 1.3 (s, 12H), 1.9-2.1 (m, 2H), 3.45 (m, 1H) 4.35 (m, 1H), 4.55 (m, 1H).

iii) 4.2 ml (4.2 mmol) of 1M lithium bis(trimethylsilyl)amide in tetrahydrofuran were added dropwise to a solution of 1.0 g (4.2 mmol) of 2-(4-fluoro-1(RS)-chlorobutyl)-4,4,5,5-tetra-

methyl-1,3,2-dioxaborolane in 7 ml of tetrahydrofuran under nitrogen at -78°C. The solution was then stirred overnight at room temperature. The solvent was removed by evaporation and the residue was taken up in diethyl ether. Insoluble material was removed by filtration and the solvent was removed by evaporation to give 1.53 g of material which was immediately redissolved in 7 ml of diethyl ether and cooled to 0°C. 0.95 ml (12.6 mmol) of trifluoroacetic acid was added and the solution was stirred at 0°C for 30 minutes. The solution was evaporated and the residue was evaporated with toluene to give 1.36 g of α(RS)-3-fluoropropyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-methylamine trifluoroacetate (1:1) as a brown oil which was used in the next step without further purification.

iv) 0.20 g (0.22 mmol) N-[N-[N-[N-[N-(tert-butoxycarbonyl)-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine was dissolved in 2 ml of dimethylformamide and 4 ml of dichloromethane. 0.2 ml (1.52 mmol) of N-methylmorpholine was added and the solution was cooled to -10°C under a nitrogen atmosphere. 40 mg (0.27 mmol) of isobutyl chloroformate were added and the solution was stirred for 10 minutes at -10°C. 0.2 g (0.44 mmol) of α(RS)-3-fluoropropyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-methylamine trifluoroacetate (1:1) was added and the mixture was stirred at room temperature for 16 hours. Dichloromethane was added and the solution was washed with 2M hydrochloric acid and water and then dried over anhydrous sodium sulphate. After evaporation there was obtained 0.21 g of N2-[N-[N-[N-[N-(tert-butoxycarbonyl)-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[4-fluoro-1(RS)-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl]-L-leucinamide in the form of a solid; MS: m/e 1017.3 $[M+H-100]^+$.

Example 61

In an analogous manner to that described in Example 4, by replacing N-[(9-fluorenyl)methoxycarbonyl]-3-(2-naphthyl)-D-

alanine with N-[(9-fluorenyl)methoxycarbonyl]-O-tert-butyl-L-α-glutamic acid and by replacing N-[(9-fluorenyl)methoxycarbonyl]-2-methyl-L-phenylalanine with N-[(9-fluorenyl)methoxy-carbonyl]-4-chloro-L-phenylalanine there was obtained 2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl-L-α-glutamyl]-4-chloro-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde as a white solid; MS: m/e 893.3 [M+H].

Example 62

In an analogous manner to that described in Example 4, by replacing N-[(9-fluorenyl)methoxycarbonyl]-3-(2-naphthyl)-D-alanine with N-[(9-fluorenyl)methoxycarbonyl]-O-tert-butyl-L-α-glutamic acid, by replacing N-[(9-fluorenyl)methoxycarbonyl]-O-tert-butyl-L-α-aspartic acid with N-(benzyloxycarbonyl)-O-tert-butyl-L-α-aspartic acid and by omitting the reaction with tert-butyl succinate there was obtained 2(RS)-[[N-[N-[N-[N-[N-(benzyloxycarbonyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde as a white solid; MS: m/e 907.4 [M+H].

Example 63

88 mg (0.09 mmol) of N2-[N-[N-[N-[N-(3-carboxy-propionyl)-L-α-aspartyl]-L-α-glutamyl]-4-chloro-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(RS)-(4,4,5,5-tetra-methyl-1,3,2-dioxoborolan-2-yl)-3-butenyl]-L-leucinamide were dissolved in 5 ml of trifluoroacetic acid and 5 ml of dichloro-methane. 5 drops of water were added and the solution was stirred at room temperature for 4 hours. The solution was diluted with toluene and evaporated. The residue was triturated with diethyl ether and the resulting solid was filtered off and dried to give 72 mg of 1(RS)-[[N-[N-[N-[N-[N-(3-carboxy-propionyl)-L-α-aspartyl]-L-α–glutamyl]-4-chloro-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-3-butenyl-boronic acid; MS: m/e 863 $[M+H-H_2O]^+$.

The starting material was prepared as follows:

i) In an analogous manner to Example 1 iii)-x), by replacing N-[(9-fluorenyl)methoxycarbonyl]-2-methyl-L-phenylalanine with N-[(9-fluorenyl)methoxycarbonyl]-4-chloro-2-methyl-L-phenylalanine there was obtained N-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-4-chloro-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine as a white solid; MS: m/e 952 $[M+H]^+$.

ii) 0.18 g (0.19 mmol) of N-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-4-chloro-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucine was dissolved in 2 ml of dimethylformamide and 5 ml of dichloromethane. 0.1 ml (0.94 mmol) of N-methylmorpholine was added and the solution was cooled to -15°C under a nitrogen atmosphere. 35 mg (0.25 mmol) of isobutylchloroformate were added and the solution was stirred for 10 minutes at -10°C. 0.12 g (0.38 mmol) α(RS)-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane-2-methylamine trifluoroacetate (1:1) was added and the mixture was stirred at room temperature for 2 hours. The solution was diluted with dichloromethane, washed with 2M hydrochloric acid and water and dried over anhydrous sodium sulphate. After evaporation there was obtained 0.18 g of N2-[N-[N-[N-[N-[3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl]-O-tert-butyl-L-α-glutamyl]-4-chloro-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(RS)-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-butenyl]-L-leucinamide in the form of a white solid; MS: m/e 1131.6 $[M+H]^+$.

iii) 166 mg (0.147 mmol) of N2-[N-[N-[N-[N-(3-(tert-butoxycarbonyl)propionyl]-O-tert-butyl-L-α-aspartyl-O-tert-butyl-L-α-glutamyl]-4-chloro-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(RS)-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)-3-butenyl]-L-leucinamide were dissolved in 5 ml of trifluoroacetic acid and 5 ml of dichloromethane. The solution was stirred at room temperature for 30 minutes, then diluted with toluene and evaporated. The residue was triturated with ether

and the resulting solid was filtered off, dried and then redissolved in 5 ml of trifluoroacetic acid and 5 ml of dichloromethane. The solution was stirred at room temperature for 30 minutes, diluted with toluene and evaporated. The residue was triturated with diethyl ether and the resulting solid was filtered off and dried to give 100 mg of N2-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-4-chloro-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-N1-[1(RS)-(4,4,5,5-tetramethyl-1,3,2-dioxoborolan-2-yl)-3-butenyl]-L-leucinamide as a white solid; MS: m/e 863 $[M+H-100]^+$.

The following Examples illustrate pharmaceutical preparations containing compounds of formula I:

Example A

Tablets containing the following ingredients may be produced in a conventional manner:

Ingredient		Per tablet
Compound of formula I		10.0 mg
Lactose		125.0 mg
Corn starch		75.0 mg
Talc		4.0 mg
Magnesium stearate		1.0 mg
	Total weight	215.0 mg

Example B

Capsules containing the following ingredients may be produced in a conventional manner:

Ingredient		Per capsule
Compound of formula I		10.0 mg
Lactose		165.0 mg
Corn starch		20.0 mg
Talc		5.0 mg
	Capsule fill weight	200.0 mg

Figure 1 - Nucleotide sequence of pMAL -NS3''Gly12 NS4A plasmid

1 CCGACACCAT CGAATGGTGC AAAACCTTTC GCGGTATGGC ATGATAGCGC

51 CCGGAAGAGA GTCAATTCAG GGTGGTGAAT GTGAAACCAG TAACGTTATA

101 CGATGTCGCA GAGTATGCCG GTGTCTCTTA TCAGACCGTT TCCCGCGTGG

151 TGAACCAGGC CAGCCACGTT TCTGCGAAAA CGCGGGAAAA AGTGGAAGCG

201 GCGATGGCGG AGCTGAATTA CATTCCCAAC CGCGTGGCAC AACAACTGGC

251 GGGCAAACAG TCGTTGCTGA TTGGCGTTGC CACCTCCAGT CTGGCCCTGC

301 ACGCGCCGTC GCAAATTGTC GCGGCGATTA AATCTCGCGC CGATCAACTG

351 GGTGCCAGCG TGGTGGTGTC GATGGTAGAA CGAAGCGGCG TCGAAGCCTG

401 TAAAGCGGCG GTGCACAATC TTCTCGCGCA ACGCGTCAGT GGGCTGATCA

451 TTAACTATCC GCTGGATGAC CAGGATGCCA TTGCTGTGGA AGCTGCCTGC

501 ACTAATGTTC CGGCGTTATT TCTTGATGTC TCTGACCAGA CACCCATCAA

551 CAGTATTATT TTCTCCCATG AAGACGGTAC GCGACTGGGC GTGGAGCATC

601 TGGTCGCATT GGGTCACCAG CAAATCGCGC TGTTAGCGGG CCCATTAAGT

651 TCTGTCTCGG CGCGTCTGCG TCTGGCTGGC TGGCATAAAT ATCTCACTCG

701 CAATCAAATT CAGCCGATAG CGGAACGGGA AGGCGACTGG AGTGCCATGT

751 CCGGTTTTCA ACAAACCATG CAAATGCTGA ATGAGGGCAT CGTTCCCACT

801 GCGATGCTGG TTGCCAACGA TCAGATGGCG CTGGGCGCAA TGCGCGCCAT

851 TACCGAGTCC GGGCTGCGCG TTGGTGCGGA TATCTCGGTA GTGGGATACG

901 ACGATACCGA AGACAGCTCA TGTTATATCC CGCCGTTAAC CACCATCAAA

951 CAGGATTTTC GCCTGCTGGG GCAAACCAGC GTGGACCGCT TGCTGCAACT

1001 CTCTCAGGGC CAGGCGGTGA AGGGCAATCA GCTGTTGCCC GTCTCACTGG

1051 TGAAAAGAAA AACCACCCTG GCGCCCAATA CGCAAACCGC CTCTCCCCGC

1101 GCGTTGGCCG ATTCATTAAT GCAGCTGGCA CGACAGGTTT CCCGACTGGA

1151 AAGCGGGCAG TGAGCGCAAC GCAATTAATG TGAGTTAGCT CACTCATTAG

1201 GCACAATTCT CATGTTTGAC AGCTTATCAT CGACTGCACG GTGCACCAAT

1251 GCTTCTGGCG TCAGGCAGCC ATCGGAAGCT GTGGTATGGC TGTGCAGGTC

1301 GTAAATCACT GCATAATTCG TGTCGCTCAA GGCGCACTCC CGTTCTGGAT

1351 AATGTTTTTT GCGCCGACAT CATAACGGTT CTGGCAAATA TTCTGAAATG

1401 AGCTGTTGAC AATTAATCAT CGGCTCGTAT AATGTGTGGA ATTGTGAGCG

1451 GATAACAATT TCACACAGGA AACAGCCAGT CCGTTTAGGT GTTTTCACGA

1501 GCACTTCACC AACAAGGACC ATAGATTATG AAAACTGAAG AAGGTAAACT

Start MBP

1551 GGTAATCTGG ATTAACGGCG ATAAAGGCTA TAACGGTCTC GCTGAAGTCG

1601 GTAAGAAATT CGAGAAAGAT ACCGGAATTA AAGTCACCGT TGAGCATCCG

1651 GATAAACTGG AAGAGAAATT CCCACAGGTT GCGGCAACTG GCGATGGCCC

1701 TGACATTATC TTCTGGGCAC ACGACCGCTT TGGTGGCTAC GCTCAATCTG

1751 GCCTGTTGGC TGAAATCACC CCGGACAAAG CGTTCCAGGA CAAGCTGTAT

1801 CCGTTTACCT GGGATGCCGT ACGTTACAAC GGCAAGCTGA TTGCTTACCC

1851 GATCGCTGTT GAAGCGTTAT CGCTGATTTA TAACAAAGAT CTGCTGCCGA

1901 ACCCGCCAAA AACCTGGGAA GAGATCCCGG CGCTGGATAA AGAACTGAAA

1951 GCGAAAGGTA AGAGCGCGCT GATGTTCAAC CTGCAAGAAC CGTACTTCAC

2001 CTGGCCGCTG ATTGCTGCTG ACGGGGGTTA TGCGTTCAAG TATGAAAACG

2051 GCAAGTACGA CATTAAAGAC GTGGGCGTGG ATAACGCTGG CGCGAAAGCG

2101 GGTCTGACCT TCCTGGTTGA CCTGATTAAA AACAAACACA TGAATGCAGA

2151 CACCGATTAC TCCATCGCAG AAGCTGCCTT TAATAAAGGC GAAACAGCGA

2201 TGACCATCAA CGGCCCGTGG GCATGGTCCA ACATCGACAC CAGCAAAGTG

2251 AATTATGGTG TAACGGTACT GCCGACCTTC AAGGGTCAAC CATCCAAACC

2301 GTTCGTTGGC GTGCTGAGCG CAGGTATTAA CGCCGCCAGT CCGAACAAAG

2351 AGCTGGCAAA AGAGTTCCTC GAAAACTATC TGCTGACTGA TGAAGGTCTG

2401 GAAGCGGTTA ATAAAGACAA ACCGCTGGGT GCCGTAGCGC TGAAGTCTTA

2451 CGAGGAAGAG TTGGCGAAAG ATCCACGTAT TGCCGCCACC ATGGAAAACG

2501 CCCAGAAAGG TGAAATCATG CCGAACATCC CGCAGATGTC CGCTTTCTGG

2551 TATGCCGTGC GTACTGCGGT GATCAACGCC GCCAGCGGTC GTCAGACTGT

2601 CGATGAAGCC CTGAAAGACG CGCAGACTAA TTCGAGCTCG AACAACAACA

2651 ACAATAACAA TAACAACAAC CTCGGGATCG AGGGAAGGAT TTCAGAATTC

EcoRI

2701 ATGGGGAGGG AGATACATCT GGGACCGGCA GACAGCCTTG AAGGGCAGGG

NS2/3 (

2751 GTGGCGACTC CTCGCGCATA TTACGGCCTA CTCTCAACAG ACGCGGGGCC

2801 TACTTGGCTG CATCATCACT AGCCTCACAG GCCGGGACAG GAACCAGGTC

2851 GAGGGGGAGG TCCAAATGGT CTCCACCGCA ACACAATCTT TCCTGGCGAC

2901 CTGCGTCAAT GGCGTGTGTT GGACTGTCTA TCATGGTGCC GGCTCAAAGA

2951 CCCTTGCCGG CCCAAAGGGC CCAATCACCC AAATGTACAC CAATGTGGAC

3001 CAGGACCTCG TCGGCTGGCA AGCGCCCCCC GGGGCGCGCT CCTTGACACC

3051 ATGCACCTGC GGCAGCTCAG ACCTTTACTT GGTCACGAGG CATGCCGATG

3101 TCATTCCGGT GCGCCGGCGG GGCGACAGCA GGGGAAGCCT ACTCTCCCCC

3151 AGGCCCGTCT CCTACTTGAA GGGCTCTTCG GGCGGTCCAC TGCTCTGCCC

3201 CTCGGGGCAC GCTGTGGGCA TCTTCCGGGC TGCCGTGTGC ACCCGAGGGG

3251 TTGCGAAGGC GGTGGACTTT GTACCCGTCG AGTCTATGGA AACCACTATG

3301 CGGTCCCCGG TCTTCACGGA CAACTCGTCC CCTCCGGCCG TATGCATGGG

Eag I

linker (

3351 AGGAGGAGGA GGAGGAGGAG GAGGAGGAGG AGGATCCATG AGCACCTGGG

BamHI

NS4A (

3401 TGCTAGTAGG CGGAGTCCTA GCAGCTCTGG CCGCGTATTG CCTGACAACA

3451 GGCAGCGTGG TCATTGTGGG CAGGATCGTC TTGTCCGGAA AGCCGGCCAT

3501 CATTCCCGAC AGGGAAGTCC TCTACCGGGA GTTCGATGAG ATGGAAGAGT

3551 GCTAGAAGCT TGGCACTGGC CGTCGTTTTA CAACGTCGTG ACTGGGAAAA

End HindIII

3601 CCCTGGCGTT ACCCAACTTA ATCGCCTTGC AGCACATCCC CCTTTCGCCA

3651 GCTGGCGTAA TAGCGAAGAG GCCCGCACCG ATCGCCCTTC CCAACAGTTG

3701 CGCAGCCTGA ATGGCGAATG GCAGCTTGGC TGTTTTGGCG GATGAGATAA

3751 GATTTTCAGC CTGATACAGA TTAAATCAGA ACGCAGAAGC GGTCTGATAA

3801 AACAGAATTT GCCTGGCGGC AGTAGCGCGG TGGTCCCACC TGACCCCATG

3851 CCGAACTCAG AAGTGAAACG CCGTAGCGCC GATGGTAGTG TGGGGTCTCC

3901 CCATGCGAGA GTAGGGAACT GCCAGGCATC AAATAAAACG AAAGGCTCAG

3951 TCGAAAGACT GGGCCTTTCG TTTTATCTGT TGTTTGTCGG TGAACGCTCT

4001 CCTGAGTAGG ACAAATCCGC CGGGAGCGGA TTTGAACGTT GCGAAGCAAC

4051 GGCCCGGAGG GTGGCGGGCA GGACGCCCGC CATAAACTGC CAGGCATCAA

4101 ATTAAGCAGA AGGCCATCCT GACGGATGGC CTTTTTGCGT TTCTACAAAC

4151 TCTTTTTGTT TATTTTTCTA AATACATTCA AATATGTATC CGCTCATGAG

4201 ACAATAACCC TGATAAATGC TTCAATAATA TTGAAAAAGG AAGAGTATGA

4251 GTATTCAACA TTTCCGTGTC GCCCTTATTC CCTTTTTTGC GGCATTTTGC

4301 CTTCCTGTTT TTGCTCACCC AGAAACGCTG GTGAAAGTAA AAGATGCTGA

4351 AGATCAGTTG GGTGCACGAG TGGGTTACAT CGAACTGGAT CTCAACAGCG

4401 GTAAGATCCT TGAGAGTTTT CGCCCCGAAG AACGTTCTCC AATGATGAGC

4451 ACTTTTAAAG TTCTGCTATG TGGCGCGGTA TTATCCCGTG TTGACGCCGG

4501 GCAAGAGCAA CTCGGTCGCC GCATACACTA TTCTCAGAAT GACTTGGTTG

4551 AGTACTCACC AGTCACAGAA AAGCATCTTA CGGATGGCAT GACAGTAAGA

4601 GAATTATGCA GTGCTGCCAT AACCATGAGT GATAACACTG CGGCCAACTT

4651 ACTTCTGACA ACGATCGGAG GACCGAAGGA GCTAACCGCT TTTTTGCACA

4701 ACATGGGGGA TCATGTAACT CGCCTTGATC GTTGGGAACC GGAGCTGAAT

4751 GAAGCCATAC CAAACGACGA GCGTGACACC ACGATGCCTG TAGCAATGGC

4801 AACAACGTTG CGCAAACTAT TAACTGGCGA ACTACTTACT CTAGCTTCCC

4851 GGCAACAATT AATAGACTGG ATGGAGGCGG ATAAAGTTGC AGGACCACTT

4901 CTGCGCTCGG CCCTTCCGGC TGGCTGGTTT ATTGCTGATA AATCTGGAGC

4951 CGGTGAGCGT GGGTCTCGCG GTATCATTGC AGCACTGGGG CCAGATGGTA

5001 AGCCCTCCCG TATCGTAGTT ATCTACACGA CGGGGAGTCA GGCAACTATG

5051 GATGAACGAA ATAGACAGAT CGCTGAGATA GGTGCCTCAC TGATTAAGCA

5101 TTGGTAACTG TCAGACCAAG TTTACTCATA TATACTTTAG ATTGATTTAC

5151 CCCGGTTGAT AATCAGAAAA GCCCCAAAAA CAGGAAGATT GTATAAGCAA

5201 ATATTTAAAT TGTAAACGTT AATATTTTGT TAAAATTCGC GTTAAATTTT

5251 TGTTAAATCA GCTCATTTTT TAACCAATAG GCCGAAATCG GCAAAATCCC

5301 TTATAAATCA AAAGAATAGC CCGAGATAGG GTTGAGTGTT GTTCCAGTTT

5351 GGAACAAGAG TCCACTATTA AAGAACGTGG ACTCCAACGT CAAAGGGCGA

5401 AAAACCGTCT ATCAGGGCGA TGGCCCACTA CGTGAACCAT CACCCAAATC

5451 AAGTTTTTTG GGGTCGAGGT GCCGTAAAGC ACTAAATCGG AACCCTAAAG

5501 GGAGCCCCCG ATTTAGAGCT TGACGGGGAA AGCCGGCGAA CGTGGCGAGA

5551 AAGGAAGGGA AGAAAGCGAA AGGAGCGGGC GCTAGGGCGC TGGCAAGTGT

5601 AGCGGTCACG CTGCGCGTAA CCACCACACC CGCCGCGCTT AATGCGCCGC

5651 TACAGGGCGC GTAAAAGGAT CTAGGTGAAG ATCCTTTTTG ATAATCTCAT

5701 GACCAAAATC CCTTAACGTG AGTTTTCGTT CCACTGAGCG TCAGACCCCG

5751 TAGAAAAGAT CAAAGGATCT TCTTGAGATC CTTTTTTTCT GCGCGTAATC

5801 TGCTGCTTGC AAACAAAAAA ACCACCGCTA CCAGCGGTGG TTTGTTTGCC

5851 GGATCAAGAG CTACCAACTC TTTTTCCGAA GGTAACTGGC TTCAGCAGAG

5901 CGCAGATACC AAATACTGTC CTTCTAGTGT AGCCGTAGTT AGGCCACCAC

5951 TTCAAGAACT CTGTAGCACC GCCTACATAC CTCGCTCTGC TAATCCTGTT

6001 ACCAGTGGCT GCTGCCAGTG GCGATAAGTC GTGTCTTACC GGGTTGGACT

6051 CAAGACGATA GTTACCGGAT AAGGCGCAGC GGTCGGGCTG AACGGGGGGT

6101 TCGTGCACAC AGCCCAGCTT GGAGCGAACG ACCTACACCG AACTGAGATA

6151 CCTACAGCGT GAGCTATGAG AAAGCGCCAC GCTTCCCGAA GGGAGAAAGG

6201 CGGACAGGTA TCCGGTAAGC GGCAGGGTCG GAACAGGAGA GCGCACGAGG

6251 GAGCTTCCAG GGGGAAACGC CTGGTATCTT TATAGTCCTG TCGGGTTTCG

6301 CCACCTCTGA CTTGAGCGTC GATTTTTGTG ATGCTCGTCA GGGGGGCGGA

6351 GCCTATGGAA AAACGCCAGC AACGCGGCCT TTTTACGGTT CCTGGCCTTT

6401 TGCTGGCCTT TTGCTCACAT GTTCTTTCCT GCGTTATCCC CTGATTCTGT

6451 GGATAACCGT ATTACCGCCT TTGAGTGAGC TGATACCGCT CGCCGCAGCC

6501 GAACGACCGA GCGCAGCGAG TCAGTGAGCG AGGAAGCGGA AGAGCGCCTG

6551 ATGCGGTATT TTCTCCTTAC GCATCTGTGC GGTATTTCAC ACCGCATATG

6601 GTGCACTCTC AGTACAATCT GCTCTGATGC CGCATAGTTA AGCCAGTATA

6651 CACTCCGCTA TCGCTACGTG ACTGGGTCAT GGCTGCGCCC CGACACCCGC

6701 CAACACCCGC TGACGCGCCC TGACGGGCTT GTCTGCTCCC GGCATCCGCT

6751 TACAGACAAG CTGTGACCGT CTCCGGGAGC TGCATGTGTC AGAGGTTTTC

6801 ACCGTCATCA CCGAAACGCG CGAGGCAGCT GCGGTAAAGC TCATCAGCGT

6851 GGTCGTGCAG CGATTCACAG ATGTCTGCCT GTTCATCCGC GTCCAGCTCG

6901 TTGAGTTTCT CCAGAAGCGT TAATGTCTGG CTTCTGATAA AGCGGGCCAT

6951 GTTAAGGGCG GTTTTTTCCT GTTTGGTCAC TTGATGCCTC CGTGTAAGGG

7001 GGAATTTCTG TTCATGGGGG TAATGATACC GATGAAACGA GAGAGGATGC

7051 TCACGATACG GGTTACTGAT GATGAACATG CCCGGTTACT GGAACGTTGT

7101 GAGGGTAAAC AACTGGCGGT ATGGATGCGG CGGGACCAGA GAAAAATCAC

7151 TCAGGGTCAA TGCCAGCGCT TCGTTAATAC AGATGTAGGT GTTCCACAGG

7201 GTAGCCAGCA GCATCCTGCG ATGCAGATCC GGAACATAAT GGTGCAGGGC

7251 GCTGACTTCC GCGTTTCCAG ACTTTACGAA ACACGGAAAC CGAAGACCAT

7301 TCATGTTGTT GCTCAGGTCG CAGACGTTTT GCAGCAGCAG TCGCTTCACG

7351 TTCGCTCGCG TATCGGTGAT TCATTCTGCT AACCAGTAAG GCAACCCCGC

7401 CAGCCTAGCC GGGTCCTCAA CGACAGGAGC ACGATCATGC GCACCCGTGG

7451 CCAGGACCCA ACGCTGCCCG AAATT

Figure 2 - Amino acid sequence of MBP-NS3''-gly$_{12}$-4A enzyme

1 MKTEEGKLVI WINGDKGYNG LAEVGKKFEK DTGIKVTVEH PDKLEEKFPQ

MBP (

51 VAATGDGPDI IFWAHDRFGG YAQSGLLAEI TPDKAFQDKL YPFTWDAVRY

101 NGKLIAYPIA VEALSLIYNK DLLPNPPKTW EEIPALDKEL KAKGKSALMF

151 NLQEPYFTWP LIAADGGYAF KYENGKYDIK DVGVDNAGAK AGLTFLVDLI

201 KNKHMNADTD YSIAEAAFNK GETAMTINGP WAWSNIDTSK VNYGVTVLPT

251 FKGQPSKPFV GVLSAGINAA SPNKELAKEF LENYLLTDEG LEAVNKDKPL

301 GAVALKSYEE ELAKDPRIAA TMENAQKGEI MPNIPQMSAF WYAVRTAVIN

351 AASGRQTVDE ALKDAQTNSS SNNNNNNNNN NLGIEGRISE FMGREIHLGP

NS2/3 (

401 ADSLEGQGWR LLAHITAYSQ QTRGLLGCII TSLTGRDRNQ VEGEVQMVST

451 ATQSFLATCV NGVCWTVYHG AGSKTLAGPK GPITQMYTNV DQDLVGWQAP

501 PGARSLTPCT CGSSDLYLVT RHADVIPVRR RGDSRGSLLS PRPVSYLKGS

551 SGGPLLCPSG HAVGIFRAAV CTRGVAKAVD FVPVESMETT MRSPVFTDNS

601 SPPAVCMGGG GGGGGGGGGS MSTWVLVGGV LAALAAYCLT TGSVVIVGRI

Linker (**NS4A (**

651 VLSGKPAIIP DREVLYREFD EMEEC

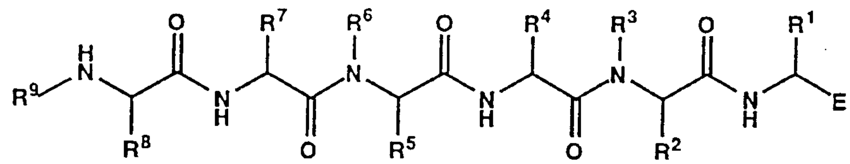
Amino acids 1-391 - Maltose binding protein and other sequences derived from New England Biolabs vector pMAL^{TM}-c2

Amino acids 393-605 and 622-675 - HCV-derived sequences (amino acids 1007-1219 and 1658-1711 of HCV polyprotein respectively)

Amino acids 606-621 - linker region

Claims

1. Compounds of the general formula



(I)

wherein

E	represents CHO or $B(OH)_2$;
R^1	represents lower alkyl, halo-lower alkyl, cyano-lower alkyl, lower alkylthio-lower alkyl, aryl-lower alkylthio-lower alkyl, aryl-lower alkyl, heteroaryl-lower alkyl, lower alkenyl or lower alkynyl;
R^2	represents lower alkyl, hydroxy-lower alkyl, carboxy-lower alkyl, aryl-lower alkyl, aminocarbonyl-lower alkyl or lower cycloalkyl-lower alkyl; and
R^3	represents hydrogen or lower alkyl; or
R^2 and R^3	together represent di- or trimethylene optionally substituted by hydroxy;
R^4	represents lower alkyl, hydroxy-lower alkyl, lower cycloalkyl-lower alkyl, carboxy-lower alkyl, aryl-lower alkyl, lower alkylthio-lower alkyl, cyano-lower alkylthio-lower alkyl, aryl-lower alkylthio-lower alkyl, lower alkenyl, aryl or lower cycloalkyl;
R^5	represents lower alkyl, hydroxy-lower alkyl, lower alkylthio-lower alkyl, aryl-lower alkyl, aryl-lower alkylthio-lower alkyl, cyano-lower alkylthio-lower alkyl or lower cycloalkyl;
R^6	represents hydrogen or lower alkyl;
R^7	represent lower alkyl, hydroxy-lower alkyl, carboxy-lower alkyl, aryl-lower alkyl, lower cycloalkyl-lower alkyl or lower cycloalkyl;
R^8	represents lower alkyl, hydroxy-lower alkyl, carboxy-lower alkyl or aryl-lower alkyl; and
R^9	represents lower alkylcarbonyl, carboxy-lower alkylcarbonyl, arylcarbonyl, lower alkylsulphonyl, arylsulphonyl, lower alkoxycarbonyl or aryl-lower

alkoxycarbonyl,
and salts of acidic compounds of formula I with bases.

2. Compounds of the general formula I according to claim 1.

3. Compounds according to claim 1, wherein R^1 represents lower alkyl, halo-lower alkyl, lower alkylthio-lower alkyl, aryl-lower alkylthio-lower alkyl, heteroaryl-lower alkyl, lower alkenyl or lower alkynyl.

4. Compounds according to claim 3, wherein the halo-lower alkyl group is fluoro-lower alkyl.

5. Compounds according to claim 3, wherein the heteroaryl-lower alkyl group is thienyl-lower alkyl or furyl-lower alkyl.

6. Compounds according to any one of claims 1 to 5, wherein R^2 represents lower alkyl, lower cycloalkyl-lower alkyl or aryl-lower alkyl.

7. Compounds according to any one of claims 1 to 6, wherein R^3 represents hydrogen.

8. Compounds according to any one of claims 1 to 5, wherein R^2 and R^3 together represent trimethylene optionally substituted by hydroxy.

9. Compounds according to any one of claims 1 to 8, wherein R^4 represents lower alkyl, lower cycloalkyl-lower alkyl, aryl-lower alkyl, aryl or lower cycloalkyl.

10. Compounds according to any one of claims 1 to 9, wherein R^5 represents aryl-lower alkyl or lower cycloalkyl.

11. Compounds according to any one of claims 1 to 10, wherein R^6 represents hydrogen.

12. Compounds according to any one of claims 1 to 11, wherein R^7 represents lower alkyl, carboxy-lower alkyl, aryl-lower alkyl or hydroxy-lower alkyl.

13. Compounds according to any one of claims 1 to 12, wherein R^8 represents hydroxy-lower alkyl, carboxy-lower alkyl or aryl-lower alkyl.

14. Compounds according to any one of claims 1 to 13, wherein R^9 represents lower alkylcarbonyl or carboxy-lower alkylcarbonyl.

15. A compound according to claim 1 selected from:

2(S)-[[N-[N-[N-[N-[N-(3-Carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]butyraldehyde;

2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4-difluorovaleraldehyde;

2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde;

2(R)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-3-(methylthio)propionaldehyde;

2(R)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-3-(butylthio)propionaldehyde;

2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4-pentenaldehyde;

2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4-pentynal;

2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-

leucyl]amino]-4-hexynal;

3-(benzylthio)-2(R)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]propionaldehyde;

2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-3-(2-thienyl)propionaldehyde;

2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-3-(3-thienyl)propionaldehyde; and

2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-3-(2-naphthyl)-D-alanyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde.

16. A compound according to claim 1, selected from:

2(RS)-[[N-[N-[N-[N-[N-(3-Carboxypropionyl)-L-seryl-D-valyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]-amino]-4,4,4-trifluorobutyraldehyde;

2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]hexanal;

(Z)-2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4-hexenal;

2(RS)-[[N-[N-[N-[N-[N-(benzyloxycarbonyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde;

2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-4-chloro-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde;

2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-D-valyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde;

2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-5-methylhexanal;

2(S)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-

α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-5-hexenal;

2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-D-norleucyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde;

2(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-D-2-cyclohexylglycyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde; and

2(RS)-[[N-[N-[N-[N-[N-(4-acetamidobenzoyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-4,4,4-trifluorobutyraldehyde;

17. A compound according to claim 1, selected from:

1(RS)-[[N-[N-[N-[N-N-(3-Carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]propylboronic acid;

1(RS)-[[N-[N-[N-[N-N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]butylboronic acid; and

1(RS)-[[N-[N-[N-[N-N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-3-butenylboronic acid.

18. A compound according to claim 1, selected from:

1(RS)-[[N-[N-[N-[N-[N-(3-Carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-4-chloro-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]-3-butenylboronic acid;

1(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-3-cyclopentyl-L-alanyl]amino]-3-butenylboronic acid;

1(R)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl]-L-leucyl]amino]pentylboronic acid;

1(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-2-methyl-L-phenylalanyl]-L-2-cyclohexylglycyl]-L-leucyl]amino]propylboronic acid;

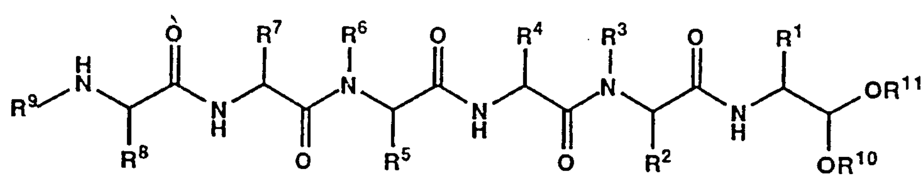
1(RS)-[[N-[N-[N-[N-[N-(3-carboxypropionyl)-L-α-aspartyl]-L-α-glutamyl]-L-2-cyclohexylglycyl]-3-methyl-L-valyl]-L-leucyl]amino]propylboronic acid; and

1(RS)-[[N-[N-[N-[N-[N-(benzyloxycarbonyl)-L-α-aspartyl]-D-valyl]-2-methyl-L-phenylalanyl]-3-methyl-L-valyl-L-leucyl]-amino]propylboronic acid.

19. A compound according to any one of claims 1 to 18 for use as a therapeutically active substance, especially as an antiviral agent and particularly as an agent against Hepatitis C, Hepatitis G or human GB viruses.

20. A process for the manufacture of a compound according to any one of claims 1 to 18 and of salts of those compounds which are acidic with bases which process comprises

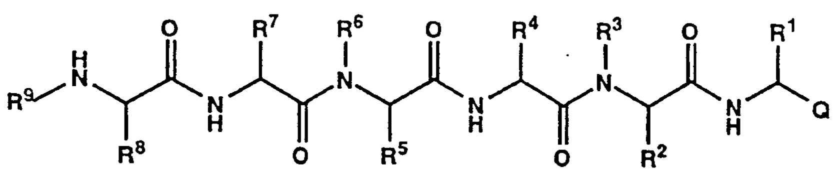
a) for the manufacture of a compound of formula I in which E represents CHO, deacetalizing and, where required, deprotecting an acetal of the general formula



(II)

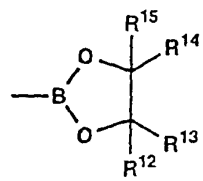
wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 have the significance given in claim 1, provided that any carboxy, hydroxy and/or aminocarbonyl group(s) present is/are in protected form, and R^{10} and R^{11} each represent lower alkyl,

b) for the manufacture of a compound of formula I in which E represents $B(OH)_2$, ring opening and, where required, deprotecting a substituted dioxaborolane of the general formula



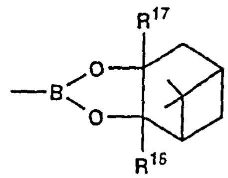
(III)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 have the significance given in claim 1, provided that any carboxy, hydroxy and/or aminocarbonyl group(s) present may be in protected form, and Q represents a group of the formula



(a)

or



(b)

wherein R^{12}, R^{13}, R^{14} and R^{15} each represent hydrogen or lower alkyl and R^{16} and R^{17} each represent hydrogen or lower alkyl,

and

c) if desired, converting an acidic compound of formula I obtained into a salt with a base.

21. A process according to claim 20, wherein the acetal of formula II or substituted dioxaborolane of formula III in which Q represents a group of formula (a) is bonded to a solid phase peptide synthesis resin.

22. Acetals of formula II given in claim 20.

23. Substituted dioxaborolanes of formula III given in claim 20.

24. A medicament, especially an antiviral medicament, particularly a medicament against Hepatitis C, Hepatitis G or human GB viruses, containing a compound according to any one of claims 1 to 18 in association with a compatible pharmaceutical carrier.

25. The use of a compound according to any one of claims 1 to 18 for the production of an antiviral medicament, especially a medicament against Hepatitis C, Hepatitis G or human GB viruses.

26. The invention as hereinbefore described.

* * *